DEVELOPMENT OF OPTIMIZED GUIDELINES FOR THERAPEUTIC STRATEGIES FOR ORGANOPHOSPHATE POISONING

THESIS

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Abstract

Organophosphates such as nerve agents have been used on several occasions in the past to inflict harm upon military and civilian populations in various parts of the world. The threat of these chemicals use against the military and civilians continues today, and the suggested treatment guidelines available may be ineffective or possibly cause harm. The guidelines investigated during the research presented here all included the use of three antidotes, atropine, oxime, and diazepam. Controversy exists over the use of oxime to treat organophosphate poisoning and various studies have concluded that they may be harmful. Both atropine and oxime are issued to military members for self-treatment following nerve agent exposure. Additionally, civilian medical facilities have access to both antidotes to treat patients exposed to nerve agents or organophosphate-based pesticides. The research presented here used a physiologically-based pharmacokinetic model to determine an optimal treatment strategy for exposures to organophosphates. Results from the model suggest that the treatment of organophosphate poisoning according to current guidance has the potential to increase the severity of symptoms that a patient is experiencing. The results presented indicate that oxime use is beneficial when the patient has been exposed to a weak organophosphate such as a pesticide, but not as prescribed in current guidance. Additionally, results indicate that in scenarios involving strong organophosphates such as nerve agents, oxime use is ineffective and has the potential to increase the severity of symptoms. Finally, the model was used to determine an optimal dosing strategy for treatment of organophosphate poisoning that varies significantly from the guidance currently available.

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DEVELOPMENT OF OPTIMIZED GUIDELINES FOR THERAPEUTIC STRATEGIES FOR ORGANOPHOSPHATE POISONING

I. Introduction

Background

The ever present threat of organophosphate and nerve agent use as weapons in military conflicts or acts of terrorism requires an effective therapeutic strategy for ushering exposed populations back to health. Organophosphates, esters of phosphoric acid, have various uses including insecticides, flame retardants, plasticizers, emulsifiers, and additives to lubricating oil (Szinicz, 2005; Cannard, 2006). Organophosphorous compounds also have use in veterinary and human medicine to treat against ticks, fleas, and lice (Karalliedde, 1999). Globally, approximately 3 million people are poisoned and 260,000 die annually from overexposure to organophosphates (Karalliedde, 1999; Aurbek, 2009). Organophosphates are a threat to military and civilian personnel in a terrorist attack, and an occupational hazard to workers exposed to organophosphate-based insecticides (Kassa, 2002).

Historically, organophosphates were first synthesized in the 19th century in France, but the development of these compounds increased significantly in Germany in the 1930s and during World War II (Szinicz, 2005). This work was initially intended to develop new insecticides, but due to these chemical's high toxicity, quickly drew the attention of the German Ministry of War (Szinicz, 2005). The nerve agents, sarin, tabun, and soman were developed from this research (Szinicz, 2005). In response, the United States, Great Britain, and Soviet Union, began researching nerve agents of their own

(Szinicz, 2005). This research led to the joint development of VX by the United States and Great Britain in the 1950s (Szinicz, 2005). Despite the high level of research and production of nerve agents during the 1940s and 1950s, these chemicals were not used in warfare or terrorism until the 1980s by Iraq, and in the 1990s by a Japanese religious cult, Aum Shinrikyo (Cannard, 2006).

Organophosphates produce their deleterious effects by inhibiting the enzyme acetylcholinesterase (AChE), which is responsible for breaking down the neurotransmitter acetylcholine (Cannard, 2006). At homeostasis, once acetylcholine is released in the synapse, it is broken down into choline and acetic acid by acetylcholinesterase (Cannard, 2006). When organophosphates are present, they bind with the acetylcholinesterase, preventing the breakdown of acetylcholine (Cannard, 2006). As a result, acetylcholine is able to continuously react with its receptor, causing the repeated stimulation of the cell (Cannard, 2006). Depending on the level of exposure, symptoms of organophosphate exposures may include miosis, blurred vision, headache, bronchoconstriction, bronchorrhea, rhinorrhea, nausea, vomiting, diarrhea, paralysis, mental instability, unconciousness, seizures, and apnea (Cannard, 2006). Respiratory failure is the leading cause of death from overexposure to organophosphates (Cannard, 2006).

The three primary antidotes for organophosphate poisoning are anticholinergics, oximes, and anticonvulsants (Cannard, 2006). The predominant anticholinergic used is atropine, which blocks acetylcholine from binding to muscarinic receptors, but is not effective at nicotinic receptors (Cannard, 2006). As a result, atropine is effective at stopping the symptoms of excessive secretions and smooth muscle stimulation, but does

not treat the effects of paralysis (Cannard, 2006). Unlike atropine, oximes help treat weakness and paralysis (Cannard, 2006). Oximes break the bond between organophosphates and acetylcholinesterase, enabling the acetylcholinesterase to resume its function of breaking down acetylcholine (Cannard, 2006). Seizures and convulsions are possible with exposures to high doses (Cannard, 2006). The anticonvulsant typically used for the treatment of seizures is diazepam (Cannard, 2006). Most armed forces use autoinjectors with atropine and an oxime for treating exposures to organophosphates (Szinicz, 2005). The U.S. military specifically uses atropine ant pralidoxime chloride (2-PAM Cl) in the autoinjectors it issues to its personnel (USAMRICD, 2007).

Several government agencies, to include the Centers for Disease Control and Prevention (CDC), the New York Department of Health (NYDH), and the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), have guidelines for administering antidotes to patients exposed to organophosphates. Each guideline recommends the use of atropine, oxime, and an anticonvulsant, but each varies in the amount of each dose as well as the timing of subsequent doses (CDC, 2008; NYDH, 2005; USAMRICD, 2007). Due to anticonvulsants treating patients by a different mechanism from that of atropine and oxime, anticonvulsants were not evaluated during the course of this research.

Many researchers have questioned the effectiveness of oxime treatment and have conducted studies to determine if they are effective or possibly harmful (Eddleston and others, 2009). Those that favor oxime treatment state that these studies have not used an adequate dose of oxime (Eddleston and others, 2009). The doubt raised in these studies needs to be investigated and a more optimal antidote dosing strategy needs to be

developed. A method to conduct such research that is cost-effective, less time consuming, and without extensive animal testing is by the use of a physiologically-based pharmacokinetic (PBPK) model (Andersen, 2003).

PBPK models use data derived from in vitro and in vivo testing to predict how a chemical will behave in a variety of scenarios (Andersen, 2003). The model uses compartments to describe different tissue groups that have similar pharmacokinetic properties (Andersen, 2003). Mass balance equations are written for each tissue and the software derives the differential equation to predict the concentration of the chemical over time (Andersen, 2003). The application of PBPK modeling with organophosphates has been investigated by several researchers and the results have shown that this method is promising in predicting how organophosphates behave in humans.

The varying treatment guidelines, as well as the questionable effectiveness of oxime treatment, led to the research conducted by Seaman (Seaman, 2008). Seaman developed a PBPK model to predict the concentration of organophosphates, atropine, oxime, acetylcholine, acetylcholinesterase, and other biological chemicals in body tissues over time (Seaman, 2008). Using this model, he was able to simulate various exposure conditions and treatment strategies (Seaman, 2008). Seaman's model was based on PBPK models developed previously to describe organophosphate exposure and acetylcholine inhibition. Among these include the models developed by Gearhart and others for diisopropylfluorophosphate (DFP) and parathion (Gearhart and others, 1994), Timchalk and others for chlorpyrifos (Timchalk and others, 2002), and Gentry and others for parathion (Gentry and others, 2002). In addition to the model developed by Seaman, other models have been developed to analyze the effectiveness of antidotes in

organophosphate poisoning. Multiple models were developed by Worek and others to demonstrate the effectiveness of oximes in nerve agent poisoning (Worek and others, 2005) and later expanded that model to incorporate the nerve agent pretreatment by carbamates such as pyridostigmine (Worek and others, 2007).

Pharmacokinetic data for organophosphates for humans is limited. Human studies with organophosphates, specifically nerve agents, would be unethical due to the high toxicity of most organophosphates. Real world exposures to include occupational exposure to insecticides and the use of nerve agents in warfare and terrorism have provided the limited human data available. These real world exposures include the use of the nerve agents sarin and tabun by Iraq against Iran in the mid-1980s, and their later use of sarin against the Kurds in 1988 (Szinicz, 2005; Cannard, 2006). Additionally, the potential for terrorist use of nerve agents exists as exhibited by a Japanese religious cult, Aum Shinrikyo, that used sarin on two occasions in Matsumoto and Tokyo in the mid-1990s (Szinicz, 2005; Cannard, 2006).

It appears that the possibility of the use of organophosphates or nerve agents in warfare has declined, but the potential still exists for its use by terrorist organizations against both military and civilian populations (Szinicz and others, 2007). Since it appears that a greater percentage of the world's population is at risk to exposure from organophosphates, there is a definite need for research into suitable antidotes and their application.

Controversy exists over the dosing and timing of atropine and pralidoxime treatment, and the use of pralidoxime for organophosphate exposure at all has been questioned (Karalliedde, 1999). Oxime treatment has been observed to be ineffective

under several situations: when the bond between the organophosphate and acetylcholinesterase has become irreversible, when acetylcholinesterase is bound by organophosphates in the system faster than it is reactivated, or when oxime treatment is stopped too soon (Szinicz, 2007). Additionally, due to the low incident rate of organophosphate poisoning, little research into developing new treatment methods or validating current methods has been performed (Szinicz, 2007). Due to the apparent controversy of oxime efficacy, additional research needs to be performed to determine appropriate dosing, timing, or if they should be used at all. This controversy and the variations in the recommendations for antidote dosing and timing from different agencies is the basis for this research.

Research objectives

1. Validate the physiologically-based pharmacokinetic (PBPK) model produced by Seaman and modify it as necessary to perform the simulations required to complete this research
2. Analyze the current therapeutic strategies using the validated PBPK model in various exposure situations to determine if they are effective or cause harm
3. Develop a set of guidelines that provides an optimal dosing and timing strategy for various exposure situations to include military, terrorist, or occupational exposures to reduce death among initial survivors and hasten full recovery.

II. Literature Review

History of organophosphates

Organophosphates are synthetically derived, and the origins of the first such compound can be traced back to the mid-1800s in France (Szinicz, 2005). The synthesis of organophosphate insecticides began in the 1930s by German chemist Gerhard Schrader (Szinicz, 2005; Cannard, 2006). Schrader's work led to the development of over 2,000 organophosphate compounds, including tabun in 1936 and sarin in 1937 (Szinicz, 2005). Schrader's work drew attention from the German Ministry of War, and approximately 200 of his compounds were recognized as potential chemical warfare agents including tabun, sarin, and soman (Szinicz, 2005; Cannard, 2006).

Germany began full production of tabun, sarin, and soman, in the 1940s (Szinicz, 2005). In response to the German research into nerve agents, research began in the United States, Great Britain, France, and the Soviet Union (Szinicz, 2005). Chemical warfare research following World War II focused on the development of nerve agents (Szinicz, 2005). Sarin was the nerve agent of choice in the United States and the Soviet Union and was stockpiled by both countries following World War II (Szinicz, 2005). Although Germany developed and possessed large quantities of nerve agents, they did not use them (Cannard, 2006). During the 1950s, insecticide companies also became interested in the potential of organophosphates (Szinicz, 2005). Also in the 1950s, joint research between Great Britain and the United States led to the development of VX, and it went into production in the United States in 1961 (Szinicz, 2005).

Nerve agents, specifically sarin and tabun, were used by Iraq during the Iraq-Iran war in the 1980s (Szinicz, 2005; Cannard, 2006). Iraq again used sarin against the Kurds

in 1988 (Szinicz, 2005; Cannard, 2006). A Japanese religious cult, Aum Shinrikyo, used sarin in multiple attacks in Matsumoto and Tokyo in 1994 and 1995, respectively (Szinicz, 2005; Cannard, 2006). In the Tokyo subway attack, only 12 of the approximately 1,000 exposed died, but the sarin used was only 30% pure and not optimally dispersed (Cannard, 2006). These real world uses have helped determine which antidotes are the most effective (Cannard, 2006).

Physiology of organophosphate poisoning

Organophosphates are esters of phosphoric acid with the most toxic being used as nerve agents in chemical warfare (Karalliedde, 1999). Organophosphates have a phosphorus atom at their center that is bound to two alkyl groups, a leaving group, and a double bond with oxygen (Cannard, 2006). The leaving group breaks off when the organophosphate bonds with an acetylcholinesterase (Cannard, 2006). Organophosphates are liquids at room temperature, but can be volatilized by a sprayer or explosion (USAMRICD, 2007). Most nerve agents are not persistent in the environment and fall below lethal concentrations fairly rapidly (Cannard, 2006). VX is not as volatile as other organophosphates, is more persistent in the environment, and poses a greater dermal hazard than other nerve agents (Cannard, 2006).

Organophosphates cause deleterious effects in the central nervous system, cardiovascular system, metabolic system, endocrine system, reproduction system, and the neuromuscular junction (Karalliedde, 1999). The probable route of exposure for an organophosphate is by inhalation, but can also occur by digestion or absorption through contact with the eye, skin, or mucous membranes (Cannard, 2006). Organophosphates

exhibit their toxic effects by binding with acetylcholinesterase, which inhibits the breakdown of acetylcholine (Aurbek and others, 2009). After a period of time, the bond between the organophosphate and acetylcholinesterase becomes permanent and is referred to as aging (Cannard, 2006). Other cholinesterase inhibitors include carbamates and other organophosphorus compounds (Cannard, 2006). Pyridostigmine bromide, a pretreatment for a potential soman exposure, is a member of the carbamate family (Cannard, 2006). The bind between a carbamate and acetylcholinesterase is reversible and breaks down naturally within one to six hours (Cannard, 2006). Once aging has occurred, acetylcholinesterase levels only recover through the production of new acetylcholinesterase, a process that may take weeks to months to occur (Cannard, 2006). In addition to acetylcholinesterase, human tissue also contains butyrylcholinesterase (BuChE) and carboxylesterase (Cannard, 2006). Organophosphates also bind to these two enzymes, but to differing affinity than acetylcholinesterase (Cannard, 2006). Additionally, the physiological effects of organophosphates binding to these two enzymes do not seem to be as critical as the binding to acetylcholinesterase (Cannard, 2006).

Physiologically, the function of butyrylcholinesterase has yet to be determined, but it has shown the ability to act as a natural defense mechanism against organophosphate poisoning (Bartling and others, 2007). The liver produces butyrylcholinesterase and releases it into the blood stream (Aurbek and others, 2009).

The human body contains two types of cholinergic receptors, muscarinic and nicotinic (Cannard, 2006). Muscarinic receptors are responsible for the stimulation of smooth muscles and exocrine glands (Cannard, 2006). They can also be found in the

central nervous system (Cannard, 2006). Muscarinic receptors stimulate lacrimal, nasal, salivary, and bronchial glands, intraocular and bronchial muscles, the heart, and bladder (Cannard, 2006). Symptoms associated with muscarinic receptor overstimulation are miosis, blurred vision, eye pain, headache, rhinorrhea, salivation, bronchorrhea, hypotension, nausea, vomiting, diarrhea, and bowel or urinary incontinence (Cannard, 2006). Nicotinic receptors are located in the neuromuscular junctions of somatic muscles as well as the autonomic ganglia (Cannard, 2006). Overstimulation of nicotinic receptors causes the repeated stimulation of individual muscle fibers, preventing the coordinated contraction of the muscles (Cannard, 2006). With the continual stimulation of the muscle fibers, fatigue and paralysis can quickly set in (Cannard, 2006). Muscarinic and nicotinic receptors are both found in the central nervous system and excessive stimulation may cause behavioral changes, coma, seizures, or central apnea (Cannard, 2006).

Onset of symptoms can present within a few seconds when exposed to a high dose or if the exposure is by inhalation (Cannard, 2006). Symptoms associated with exposure by inhalation typically peak 15 to 30 minutes following exposure (Cannard, 2006). Inhalation of organophosphates is typically the most lethal route of exposure due to the distribution systemically through the circulatory system and death can occur within seconds (Cannard, 2006). Generally, survival rates are high if the patient withstands the first 30 minutes following exposure (Cannard, 2006). Symptoms associated with a dermal exposure may be delayed up to 18 hours (Cannard, 2006). Consequently, without an accurate exposure history from the patient, dermal exposures may not be accurately diagnosed (Cannard, 2006). Dermal exposures will also likely exhibit symptoms localized to the area of exposure (Cannard, 2006).

During organophosphate poisoning, the acetylcholinesterase enzyme is phosphorylated, producing an organophosphate-acetylcholinesterase complex (Thiermann and others, 1999). This complex exhibits the potential to release the acetylcholinesterase naturally without the use of any medical treatment (Thiermann and others, 1999). The process of aging occurs when the organophosphate-acetylcholinesterase complex loses a hydroxyl group, preventing the complex from breaking down either naturally or with medical treatment (Thiermann and others, 1999). Oxime-induced degradation of the organophosphate-acetylcholinesterase complex occurs in a two-step process; the first step produces a phosphorylenzyme-oxime complex that is followed by the second step of releasing acetylcholinesterase (Thiermann and others, 1999). The potential exists for oxime treatment to produce phosphorylated oximes, which are cholinesterase inhibitors as well (Karalliedde, 1999).

The level of acetylcholinesterase activity shows a good correlation with the level of symptoms exhibited by the patient (Ashani and Pistinner, 2004). An acetylcholine level of 35% of the basal level would likely cause symptoms associated with organophosphate poisoning, and an acetylcholinesterase level of 10% of the basal level is required to maintain physiological responses in the brain and diaphragm (Ashani and Pistinner, 2004).

Antidotes

The physiological effects of organophosphate exposure were discovered by Germany, Great Britain, and the United States during World War II (Szinicz, 2005). The Germans discovered that atropine was an effective antidote to organophosphate exposure

and used it to treat exposures during research and production during World War II (Szinicz, 2005). The United States Army began using an autoinjector with atropine in the 1950s (Szinicz, 2005). Most armed forces today use autoinjectors with atropine and an oxime (Szinicz, 2005). A patient's recovery from organophosphate exposure requires treatment within a few hours due to the bond between organophosphates and acetylcholinesterase becoming irreversible (Cannard, 2006). Early diagnosis of organophosphate poisoning is critical to the survival of the patient; however, due to the rarity of organophosphate poisoning, it is often misdiagnosed (Cannard, 2006).

Atropine effectively treats organophosphate poisoning by competing with abundant acetylcholine at the muscarinic receptors, but has not shown to be effective at nicotinic receptors such as at the neuromuscular junction (Karalliedde, 1999). Atropine treatment does not reverse miosis, therefore the size of the pupil should not be used as a method to determine efficacy of treatment (Cannard, 2006). Atropine is effective at crossing the blood-brain barrier and acts to counteract the effects of excess acetylcholine in the central nervous system (Karalliedde, 1999). Atropine therapy has proven to be a successful antidote and has reduced the mortality from exposure to organophosphates (Karalliedde, 1999). The traditional initial dose of atropine is 2–6 mg by either intravenous or intramuscular injection, although intravenous is preferred if it is available (Cannard, 2006). Atropine itself is toxic and personnel that receive small amounts, 2 mg, without organophosphate poisoning may exhibit a reduction in secretions, sedation, a reduction in digestive motility, and tachycardia (USAMRICD, 2007). Larger doses of atropine on the order of 10 mg, may produce delirium in patients (USAMRICD, 2007).

Once the bond between organophosphate and acetylcholinesterase matures, oximes lose their effectiveness and are unable to break the bond (Cannard, 2006). Acetylcholinesterase recovers fairly slowly in the body at a rate of approximately 1% per day (Karalliedde, 1999). Each organophosphate ages at different rates; soman has an aging half time of two to six minutes while other nerve agents have aging half times from five to 48 hours (Cannard, 2006). Due to the rapid aging of soman, oxime treatment will likely be ineffective since the bonds will be irreversibly bound before medical treatment can commence (Cannard, 2006). Oximes typically do not affect symptoms associated with muscarinic receptors, thus oxime treatment is likely not necessary with mild exposures (Cannard, 2006). The oxime used in the United States is pralidoxime chloride, or 2-PAM Cl (2-pyridinealdoxime methiodide chloride) (Cannard, 2006).

A potential side-effect of oxime treatment is hypertension (Cannard, 2006). Pralidoxime treatment can produce deleterious effects to include drowsiness, headache, vision problems, nausea, dizziness, tachycardia, hyperventilation, and muscular weakness (Kassa, 2002). The most common cause of death in oxime poisoning is respiratory paralysis (Kassa, 2002).

Based on early data, an oxime plasma concentration of 4 μg/mL was determined the amount necessary to reverse organophosphate symptoms, but later data has raised doubt upon this value (Kassa, 2002). Several factors are responsible for the efficacy of oxime therapy, including the specific organophosphate, the route of exposure, and the route and timing of oxime treatment (Kassa, 2002). Pralidoxime appears to be much more effective against insecticides than nerve agents (Kassa, 2002). Pralidoxime is not considered to be effective enough against nerve agents, but newly developed oximes, HI-

6 and HLö-7, have demonstrated better ability to protect against nerve agents and increase survivability (Kassa, 2002). Pralidoxime is stable as an aqueous solution, enabling it be stored in solution; HI-6 and HLö-7 are not stable in water and must be stored as a powder until needed (Kassa, 2002). The oximes pralidoxime, obidoxime, and HI-6, are available as an auto-injector for use in the field (Kassa, 2002).

There is a lack of evidence that supports how effective the current treatment methods are for organophosphate poisoning (Szinicz, 2007). Due to the low incident rate of organophosphate poisoning, little research has gone into developing new treatment methods or verifying how effective current treatment methods are (Szinicz, 2007). *In vitro* studies have demonstrated the potential for oximes to be an effective treatment for organophosphate poisoning, but in actual practice with exposed victims, oximes have been less effective or even harmful (Szinicz, 2007). At large doses, pralidoxime itself has been shown to inhibit acetylcholinesterase (Karalliedde, 1999). The use of an oxime without the use of atropine has shown minimum effectiveness (Szinicz, 2007). The blood-brain barrier hinders the passage of oximes and limits their effectiveness in the brain (Karalliedde, 1999). Pralidoxime is most effective at the neuromuscular junction, but is not effective at muscarinic receptors (Karalliedde, 1999). Additionally, the effectiveness of oximes may be dependent on the dose of atropine that has been administered (Szinicz, 2007).

The reactivation of acetylcholinesterase is dependent on the efficacy of the oxime treatment, the rate the bond between acetylcholinesterase and organophosphate ages, and the rate of natural reversal of the bonding (Szinicz, 2007). Oxime effectiveness can be evaluated by how well the patient recovers their neuromuscular functions (Szinicz, 2007).

Acetylcholinesterase can be inhibited by both persistent organophosphates remaining in the system, or by organophosphates that are freed when oximes break the acetylcholinesterase-organophosphate bond (Szinicz, 2007). The dose required for an oxime to produce beneficial results is dependent on the type of organophosphate (Thiermann and others, 1999). The rate of reactivation of the enzymes, acetylcholinesterase and butyrylcholinesterase, is dependent on the type of enzyme, the oxime used, and the organophosphate to which exposed (Bartling and others, 2007).

The use of clonidine and fluoride treatment for organophosphate poisoning has provided promising results and further research into their applicability is required (Karalliedde, 1999). According to Karalliedde, the therapeutic methods in place have not produced acceptable results and need to be revisited (Karalliedde, 1999).

In research performed by Aurbek and others, it was determined that oxime treatment was less effective in reactivating butyrylcholinesterase than acetylcholinesterase (Aurbek and others, 2009). The researchers were able to show that organophosphates reacted with acetylcholinesterase and butyrylcholinesterase at similar rates, and butyrylcholinesterase is an effective defense against organophosphate poisoning (Aurbek and others, 2009).

Current therapeutic recommendations

Various organizations, including the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), and the New York Department of Health (NYDH), have therapeutic guidelines for the treatment of organophosphate exposures.

Each agency's guideline varies in the amount of each dose and the timing of dosing (Cannard, 2006).

The CDC provides recommendations for the administering of nerve agent antidotes to emergency responders and to hospital medical staff (CDC, 2010). Emergency responders are advised to administer 2 to 4 mg of atropine and 600 mg of pralidoxime intramuscularly for mild to moderate symptoms (CDC, 2010). For severe symptoms, 6 mg of atropine and 1,800 mg of pralidoxime intramuscularly are recommended (CDC, 2010). The CDC considers mild to moderate symptoms to include localized sweating, muscle twitching, nausea, vomiting, muscle weakness, and dyspnea (CDC, 2010). Unconsciousness, convulsions, apnea, and paralysis are classified as severe symptoms by the CDC (CDC, 2010). A repeat dose of 2 mg of atropine is recommended every 5 to 10 minutes until breathing becomes normal and reduction in secretions have occurred (CDC, 2010). The CDC does not provide guidance for repeat doses of pralidoxime (CDC, 2010).

The CDC's recommendations for emergency department staff vary slightly from their recommendations in the field. The recommendation for atropine dosing and timing are identical to the recommendation to emergency responders (CDC, 2010). Pralidoxime therapy does vary with a recommended dose of 15 mg/kg (approximately 1,000 mg for adults) given slowly intravenously (CDC, 2010). This dose does not vary, regardless of the severity of symptoms (CDC, 2010). The CDC does not provide guidance to hospital staff on subsequent dosing of pralidoxime (CDC, 2010).

The NYDH has also developed a set of recommendations for emergency responders and emergency department personnel. For mild to moderate symptoms,

which include sweating, muscle twitching, nausea, vomiting, weakness, and shortness of breath, the NYDH recommends an initial atropine dose of 2 to 4 mg intramuscularly or intravenously and 600 mg of pralidoxime chloride intramuscularly or a slow infusion of 25 mg/kg intravenously (NYDH, 2005). NYDH recommends repeating atropine every 2 to 5 minutes until secretions and breathing have returned to close to normal (NYDH, 2005). An additional pralidoxime dose is recommended at 30 to 60 minutes, then hourly for 1 or 2 additional doses (NYDH, 2005). The quantity for repeat doses of neither atropine nor pralidoxime are clearly identified (NYDH, 2005).

The NYDH provides an additional set of measures for severe exposures, which according to the NYDH include unconsciousness, seizures, apnea, and paralysis (NYDH, 2005). The recommendations for severe exposures are 6 mg of atropine intramuscularly and either 1800 mg of pralidoxime intramuscularly or 50 mg/kg by slow intravenous infusion (NYDH, 2005). Additional dosing follows the same recommendations as mild and moderate exposures (NYDH, 2005).

USAMRICD provides treatment recommendations to military personnel in the field and to medical personnel in field hospitals (USAMRICD, 2007). USAMRICD recommends a symptoms-based treatment strategy (USAMRICD, 2007). Military personnel in the field are issued three MARK I Kits (USAMRICD, 2007). Each kit contains two auto-injectors, one with 2 mg of atropine and one with 600 mg of pralidoxime chloride (USAMRICD, 2007). A replacement for the MARK I Kit has been developed in the form of the Antidote Treatment – Nerve Agent, Auto-injector (ATNAA) (FDA, 2006). The ATNAA contains 2.1 mg of atropine and 600 mg of pralidoxime in separate chambers of a single auto-injector that sequentially injects the antidotes through

a single needle (FDA, 2002). For military personnel in the field, their guidance recommends the self-administration of one MARK I Kit if the individual is experiencing effects from nerve agent exposure (USAMRICD, 2007). An additional MARK I Kit is recommended if there is no improvement within 10 minutes (USAMRICD, 2007). For severe exposures where the individual is unable to self-administer antidote, a bystander should administer all three MARK I Kits to the exposed individual and any additional treatment would not be administered until the individual arrives at a medical facility (USAMRICD, 2007).

Medical personnel are advised to administer one MARK I Kit if the casualty is experiencing miosis and severe rhinorrhea (USAMRICD, 2007). One or two doses are recommended for mild to moderate dyspnea (USAMRICD, 2007). For severe exposures, USAMRICD recommends the immediate administering of three MARK I Kits (USAMRICD, 2007). Subsequent dosing of atropine is recommended based on the level of secretions and necessity of assisted ventilation (USAMRICD, 2007). A 2 mg dose repeated every three to five minutes is recommended by the intravenous (IV) route until ventilation is no longer required (USAMRICD, 2007). USAMRICD recommends oxime therapy to continue for two to three additional doses every hour (USAMRICD, 2007). They recommend that 1 gram of oxime be administered via IV over a 20 to 30-minute period (USAMRICD, 2007). In lieu of IV availability, USAMRICD recommends three pralidoxime auto-injectors (USAMRICD, 2007).

The WHO recommends an oxime treatment strategy with an initial dose of 30 mg/kg (approximately 2,000 mg for an adult) and subsequent doses of 8 mg/kg (approximately 500 mg for an adult) every hour (Eddleston and others, 2009). The

dosing recommendations for antidote treatment from the CDC, NYDH, and USAMRICD are shown in Table 1 and Table 2.

Table 1. Antidote recommendations for mild/moderate symptoms

		CDC (field)	CDC (hospital)	NYDH	USAMRICD (field)	USAMRICD (hospital)
Atropine	Initial Dose	2 – 4 mg	2- 4 mg	2 – 4 mg	2 mg	2 - 4 mg
	Repeat Dose	2 mg	2 mg	Not specified	2 mg	No instructions
	Repeat Interval	5 – 10 min	5 – 10 min	2 – 5 min	10 min	No instructions
Pralidoxime	Initial Dose	600 mg	1000 mg	600 mg	600 mg	600 – 1200 mg
	Repeat Dose	No instructions	No instructions	Not specified	600 mg	No instructions
	Repeat Interval	No instructions	No instructions	30 – 60 min, then hourly	10 min	No instructions

(CDC, 2010; NYDH, 2005; USAMRICD, 2007)

Table 2. Antidote recommendations for severe symptoms

		CDC (field)	CDC (hospital)	NYDH	USAMRICD (field)	USAMRICD (hospital)
Atropine	Initial Dose	6 mg	6 mg	6 mg	6 mg	6 mg
	Repeat Dose	2 mg	2 mg	Not specified	Not applicable, only 6 mg carried in field	2 mg
	Repeat Interval	5 – 10 min	5 – 10 mg	2 – 5 min	Not applicable	3 – 5 min
Pralidoxime	Initial Dose	1800 mg	1000 mg	1800 mg	1800 mg	1800 mg
	Repeat Dose	No instructions	No instructions	Not specified	Not applicable, only 1800 mg carried in field	1000 mg
	Repeat Interval	No instructions	No instructions	30 – 60 min, then hourly	Not applicable	60 min

(CDC, 2010; NYDH, 2005; USAMRICD, 2007)

Human oxime studies

Pralidoxime treatment for organophosphate poisoning has raised doubt as to how effective it may be, and studies have even concluded that it may be harmful (Eddleston and others, 2009). Others have stated that the dosing used in these studies was too low and suggested a higher dose should be used, such as the dose recommended by the WHO (Eddleston and others, 2009). A randomized controlled trial conducted by Eddleston and

others challenged the efficacy of pralidoxime in organophosphate insecticide poisoning (Eddleston and others, 2009). They compared the results of a group receiving the WHO-recommended dose of pralidoxime against a control group receiving a placebo (Eddleston and others, 2009). Pralidoxime was successful at reactivating acetylcholinesterase in the blood compared to no reactivation occurring with the control group (Eddleston and others, 2009).

Despite this reactivation of acetylcholinesterase, the researchers found that pralidoxime treatment resulted in a 69% increase in mortality (Eddleston and others, 2009). They concluded that the dose of pralidoxime recommended by the WHO "is most likely to be ineffective, and may be harmful" (Eddleston and others, 2009). The researchers questioned that the dose may be too high, and may be more beneficial at lower doses (Eddleston and others, 2009). The dose level recommended by the WHO is based on levels that are effective in *in vitro* studies and that the dose may not be the best *in vivo* dose for humans (Eddleston and others, 2009). The researchers recommend that further study be conducted to find an effective oxime dose for use in human organophosphate poisoning (Eddleston and others, 2009).

PBPK Modeling

Physiologically-based pharmacokinetic (PBPK) modeling calculates the concentrations of chemicals over time in different tissues of the body. The model contains physiological properties such as tissue volume, blood flow rate, and metabolic pathways. PBPK models must also contain properties of the modeled chemical to include tissue solubility, metabolic rates, and routes of exposure (Andersen, 2003).

Mass balance equations are numerically integrated for each tissue to determine the concentration in the respective tissue over time. Concentrations of particular chemicals in different tissues is dependent on pulmonary rate, tissue volume, tissue blood flow rate, tissue partition coefficients, and metabolic rates of the chemical in different tissues. PBPK model parameters such as partition coefficients and metabolic rates are determined from extensive in vitro studies. The use of PBPK modeling requires less funding, time, and animal subjects than traditional studies. PBPK models can be validated by conducting similar in vivo experiments and comparing the data to the model output (Andersen, 2003).

PBPK modeling uses data for absorption, distribution, metabolism, and excretion of a chemical within the body. In vivo animal studies typically supply the required data for absorption, distribution, and excretion. Metabolism data can often be estimated by fitting the model results to pharmacokinetic data. Absorption into the body can occur through ingestion, inhalation, or dermal absorption. Elimination of the chemical can occur through excretion in the urine or feces, exhalation, or metabolism (Hoang, 1995).

The PBPK model used to conduct the research in this thesis assumes that chemical concentration within a tissue is homogenous and uses ordinary differential equations with respect to time to calculate the quantity of a chemical. Partition coefficients are used within the mass balance when partitioning occurs within the tissue. (Hoang, 1995).

Metabolism is a complex mechanism, but is implemented into PBPK models in the form of zero order, first order, or Michaelis-Menten kinetics. The V_{max} and K_m required in the Michaelis-Menten equation are derived from *in vitro* and *in vivo*

measurements. Most PBPK models make the assumptions that chemical transport is limited by flow, assumes a homogenous chemical concentration within a tissue group, and that metabolism occurs in the liver and follows Michaelis-Menten kinetics (Hoang, 1995).

PBPK modeling of organophosphates

The consideration of developing a PBPK model to estimate organophosphate behavior in the body can be traced to a study conducted by Maxwell and others in 1987 (Maxwell and others, 1987). That study looked at the inhibition of cholinesterase by soman in various organs and plasma of rats. To determine important factors related to the *in vivo* and extent of cholinesterase inhibition, the researchers used a multiple regression model. From the regression model, the researchers determined that blood flow, carboxylesterase, and cholinesterase, accounted for 94% of the variability (Maxwell and others, 1987). Blood flow accounted for 79% of the variation, leading to the hypothesis that a PBPK model could be used to model the kinetics of soman influence on *in vivo* cholinesterase inhibition (Maxwell and others, 1987).

In 1988, Maxwell and others furthered their research into the development of a pharmacodynamic model to determine the behavior of soman and acetylcholinesterase in rats. Their model determined that the metabolism of soman in plasma contributed the most to changes in soman inhibition of acetylcholinesterase in the brain (Maxwell and others, 1988).

Gearhart and others developed a PBPK model to describe how diisopropyfluorophosphate (DFP) affects acetylcholinesterase inhibition in mammals

(Gearhart and others, 1990). The researchers used the model to look at the effects of repeated and prolonged exposures on acetylcholinesterase levels, a scenario that would be similar to an occupational setting. The researchers concluded that this type of model may be useful for modeling organophosphate exposures in humans (Gearhart and others, 1990).

In 1994, Gearhart and others took the next step in PBPK modeling and developed a model for organophosphate exposure and acetylcholinesterase inhibition in humans (Gearhart and others, 1994). The researchers developed the model to look at two different organophosphates, DFP and parathion. DFP was chosen to act as a surrogate for other organophosphates such as nerve agents due to DFP having a similar behavior to these agents. The model of parathion also had to include the metabolism of parathion to its more toxic metabolite, paraoxon. The model parameters were determined from in vivo data from rats and then scaled for humans. Both models were validated by comparing the model results to literature data from exposures to these chemicals. The researchers concluded that this type of model could be used for other organophosphates as well (Gearhart and others, 1994).

In 1997, Langenberg and others developed a physiologically-based model to investigate the behavior of two different types of stereoisomers of soman (Langenberg and others, 1997). Different stereoisomers of soman exhibit different levels of toxicity and was the basis for the research conducted by Langenberg and others. Their research led to the suggestion of expanding the model to four of the stereoisomers due to large variances in the biochemistry of the two groups that were initially investigated (Langenberg and others, 1997).

Timchalk and others developed a PBPK model in 2002 for chlorpyrifos, the active ingredient in some commercially available pesticides (Timchalk and others, 2002b). The researchers used experimental data from rats and humans exposed to chlorpyrifos along with literature data to construct a model that exhibited the behavior seen in the experimental trials. Their model was capable of describing human and rat response to chlorpyrifos exposure fairly well under acute and chronic exposures, as well as oral and dermal exposures. The researchers concluded that the PBPK model used in the study would be a good starting point for other organophosphates models and could be used to perform risk assessments under multiple exposure scenarios. In a later study, Timchalk and others used the PBPK model for chlorpyrifos to perform a Monte Carlo analysis of variability between individuals with regards to model inputs (Timchalk and others, 2002a). The researchers exhibited the ability of a PBPK model to determine the impact of variability amongst the model inputs when conducting a risk assessment (Timchalk and others, 2002a).

In 2002, Gentry and others performed a similar analysis with the PBPK model for parathion developed by Gearhart and others (Gentry and others, 2002). The researchers performed a Monte Carlo analysis to develop a method to evaluate how polymorphism in genes relates to dose variances in different tissues. Like Timchalk and others, Gentry and others came to the conclusion that using a PBPK model with a Monte Carlo analysis is a useful method to characterize variances in tissue doses (Gentry and others, 2002).

Poet and others developed and validated a PBPK model in 2004 to describe the behavior of another organophosphate pesticide, diazinon (Poet and others, 2004). This model was based on the PBPK model built in 2002 by Timchalk and others for

chlorpyrifos. The model developed by Gearhart and others in 1990 was also used during the development of their model. The researchers were able to show that the PBPK model developed for diazinon was capable of estimating tissue concentrations and relating inhibition of cholinesterase to metabolism (Poet and others, 2004). This model is yet another example of the usefulness of PBPK modeling of organophosphate poisoning.

A model developed in 2004 by Ashani and Pistinner described the inhibition of acetylcholinesterase and butyrylcholinesterase by the nerve agents VX, soman, and sarin (Ashani and Pistinner, 2004). The goal of the study was to determine the effectiveness of administering exogenous butyrylcholinesterase to bind with free nerve agent molecules in plasma. The model developed was able to demonstrate that pretreatment with human butyrylcholinesterase should prevent symptoms of organophosphate poisoning (Ashani and Pistinner, 2004).

Another PBPK model published in 2004 demonstrated the ability of PBPK modeling to handle interactions between multiple chemicals (El-Masri and others, 2004). The researchers developed the model to analyze the interaction between chlorpyrifos and parathion, as well as the metabolites of these two organophosphates, chlorpyrifos-oxon and paraxon respectively. The model was composed of four PBPK models, one for each chemical of interest, with the models for the main chemicals and its metabolite linked at the liver (El-Masri and others, 2004). The researchers were able to demonstrate that a PBPK model can successfully be applied to multiple chemicals (El-Masri and others, 2004), an important consideration for modeling an organophosphate and its antidotes in a single model.

In 2005, Worek and others developed a model to demonstrate the effectiveness of different oximes in nerve agent poisoning (Worek and others, 2005). The researchers built the model to look at the effectiveness of the oximes, obidoxime, pralidoxime, and HI 6, in response to poisoning by sarin, cyclosarin, and VX. The model was validated by comparing the acetylcholinesterase levels predicted by the model to *in vivo* levels measured in a patient poisoned by parathion and treated with atropine and obodoxime. The researchers concluded that a dynamic model would be a capable tool for comparing various oximes, determining effective oxime concentrations, and for developing oxime treatment for organophosphate poisoning (Worek and others, 2005). This emphasizes that accurate parameter values are needed for the oxime being used to ensure that the model output reflects what happens in a living environment.

In 2006, the same group of researchers led by Aurbek, developed a model to look specifically at the effectiveness of the oxime HI 6 in VX poisoning (Aurbek and others, 2006). In 2007, the researchers led by Worek, expanded the model developed in 2005 to incorporate pretreatment by a carbamate such as pyridostigmine (Worek and others, 2007). Both sets of researchers show that the effectiveness of medical treatment for organophosphate poisoning can be analyzed with a PBPK model.

Seaman developed a PBPK model in 2008 to describe the behavior of organophosphates and their antidotes, atropine and oxime, in humans (Seaman, 2008). His research aimed at determining the effectiveness of the antidotes that are widely used in practice. He concluded that oximes were more effective when used against less toxic organophosphates such as commonly used insecticides, but less effective, or even

harmful, when the organophosphates had a higher toxicity, such as nerve agents (Seaman, 2008).

III. Methodology

Modeling Structure

The model simulations used during this research were performed with version 9.0 of STELLA®, modeling software developed by isee Systems, Inc. The model consisted of compartments for pulmonary, arterial, venous, brain, diaphragm, liver, fat, slowly perfused, richly perfused, thigh, and kidney tissues. The model described the absorption, distribution, metabolism, and excretion of organophosphates, atropine, and oxime. Additionally, the model describes the behavior of acetylcholine, acetylcholinesterase, butyrylcholinesterase, and carboxylesterase. The basic structure of the model is shown in Figure 1.

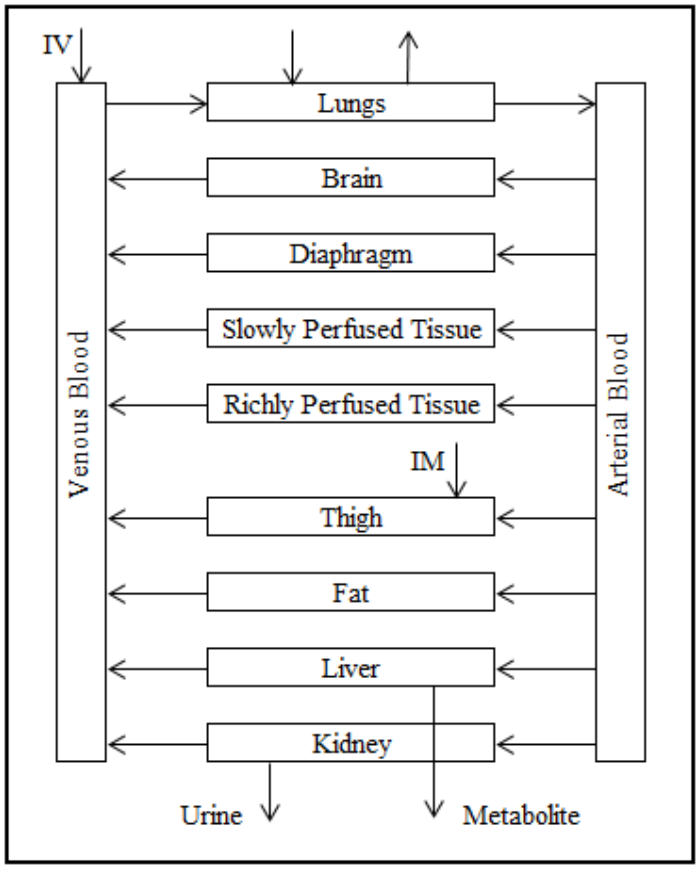

Figure 1 - Simplified model structure

Organophosphates were absorbed through inhalation into the pulmonary tissue and distributed through the arterial tissue to the rest of the system. Atropine and oxime were absorbed by either intramuscular injection in thigh tissue or through intravenous injection in venous tissue. Atropine and oximes were eliminated either through metabolism by enzymes in the liver or excretion in the urine from the kidneys. Acetylcholine and the esterases were naturally produced and degraded in each of the different tissue compartments.

Organophosphates, atropine, oxime, acetylcholine, and esterases interacted throughout the model through chemical reactions with one another. Complexes involving organophoshates and the three esterases were also described by the model in each of the tissues. Literature has indicated that following the reaction between the organophosphate-esterase complex with oxime, a complex of consisting of the organophosphate and oxime is formed. This complex has been described to be an acetylcholinesterase inhibitor as well (Worek and others, 2004). For model simplification, these complexes and pure organophosphate molecules were aggregated into solely organophosphate molecules.

Equations

A full list of equations used with the model can be found in Appendix A. A mass balance equation for each of the chemical components, organophosphates, atropine, oxime, acetycholine, and the three esterases, is calculated for each tissue compartment. The general form for each mass balance equation is shown in equation 1.

$$Accumulation = In - Out + Generation - Consumption \quad (1)$$

Inflows into the system can consist of inhalation in the lungs, intramuscular injection in the thigh tissue, or intravenous injection in the venous tissue. The primary inflow into each tissue compartment is from the arterial blood compartment. Outflows from the system are exhalation from the lungs, elimination in the urine, or metabolism. The primary outflow in each tissue compartment is blood flow out to the venous compartment.

Generation and consumption occur in the tissue compartments through natural synthesis and degradation as well as through chemical reactions between the different chemical components. The natural synthesis of esterases was zero-order and represented in each tissue by a synthesis constant. Degradation of esterases was represented by a first-order process and was dependent on the esterase concentration within the tissue compartment. The overall esterase concentration in each tissue was determined by equation 2.

$$d[Esterase]/dt = Synthesis\ constant - Degradation\ constant * [Esterase] \quad (2)$$

The interaction between the organophosphates and esterases are represented by the following chemical reaction.

$$OP + Esterase \underset{k_s}{\overset{k_i}{\rightleftharpoons}} OP/esterase\ complex \xrightarrow{k_a} Aged\ OP - esterase\ complex \quad (3)$$

where

k_i = OP reaction rate coefficient with esterase (mol^{-1} $time^{-1}$)

k_a = OP-esterase complex aging reaction rate coefficient ($time^{-1}$)

k_s = OP-esterase complex natural separation reaction rate coefficient ($time^{-1}$)

This chemical reaction is represented by the following differential equation.

$$\frac{d[Esterase/OP]}{dt} = k_i[Esterase][OP] - k_s[Esterase/OP\ ] - k_a[Esterase/OP] \quad (4)$$

The interaction between the complex of OP and esterase with oxime is represented by the following chemical reaction.

$$OP/esterase\ complex + oxime \xrightarrow{k_r} OP + Esterase + Oxime \quad (5)$$

where

k_r = OP-esterase complex reaction rate coefficient with oxime (mol^{-1} $time^{-1}$)

This chemical reaction is represented by the following differential equation.

$$\frac{d[Esterase/OP]}{dt} = -k_r[Esterase/OP][Oxime] \quad (6)$$

The relationship between acetylcholine actively stimulating the nerve, acetylcholinesterase, and atropine is shown in equation (7). The equation incorporates the effect atropine has on blocking the excess acetylcholine present in the synapse through the use of a ratio that decreases the rate of nerve stimulation by acetylcholine at the nerve receptors as the concentration of atropine increases. The reaction between acetylcholine and acetylcholinesterase is represented by a second-order reaction (Seaman, 2008).

$$\frac{d[active\ ACh]}{dt} = p_1\left\{\frac{p_1}{p_1+[Atropine]}\right\} - p_2[AChE][active\ ACh] \quad (7)$$

where

p_1 = acetylcholine binding rate (mass / time)

p_2 = acetylcholine degradation constant ($time^{-1}$)

This equation simplifies to equation (8) when no atropine is present in the system.

$$\frac{d[active\ ACh]}{dt} = p_1 - p_2[AChE][active\ ACh] \quad (8)$$

The model makes extensive use of a model output that is referred to as a symptom curve. This output was developed to express the severity of symptoms that the patient is experiencing. The value of the symptom curve is a ratio of the concentration of acetylcholine molecules that are actively stimulating the nerves over the concentration of active acetylcholine molecules at homeostasis. When an organophosphate is introduced into the system, it binds with acetylcholinesterase molecules and prevents the breakdown of acetylcholine, causing the ratio and the symptom curve level to increase. Introduction of atropine effectively blocks the nerve receptor cites, preventing acetylcholine from reaching these sites, effectively lowering this ratio and the symptom curve. At homeostasis with no atropine or organophosphates present in the system, the symptom curve has a value of one. The metric derived from the differential equation shown in equation (9) was one of the key metrics used to compare different treatment strategies. This metric evaluates symptoms at a particular point in time by comparing the concentration of acetylcholine at the nerve receptor sites to the basal concentration of acetylcholine at these sites. While this metric provided an indication of the level of symptoms at any given time, in order to determine the overall effectiveness of a treatment over the course of the simulation, an additional metric was developed.

$$\frac{d\ Symptoms}{dt} = \frac{[ACh\ site]}{[Basal\ ACh\ site]} \quad (9)$$

As shown in equation (10), treatment effectiveness will be evaluated by calculating the time weighted average of the symptom curve with organophosphate exposure and antidote treatment and comparing it against the time weighted average of

the symptom curve with no exposure or treatment (Merrill and others, 2009). It is simply a ratio of the area between the symptom curve and baseline of the simulation with an exposure and treatment over the area between the symptom curve and baseline of a patient without exposure or treatment. Both the numerator and denominator of the ratio have units of hours, thus the normalized symptom curve area is a unitless number.

$$Normalized\ symptom\ curve\ area = \frac{\int_{T_1}^{T_2} Symptoms_A\ dt}{\int_{T_1}^{T_2} Basal\ Symptoms\ dt} \quad (10)$$

Using this method, a patient with no exposure or treatment has a normalized symptom curve area of 1.0. The higher the value of the symptom curve area, the more harmful a particular scenario was to a patient.

Assumptions

There are several assumptions that are made with respect to the modeling of a living system. As in most PBPK models, the model assumes instantaneous mixing and equilibrium of the different chemicals within a particular tissue. Specifically to this model, metabolism of the chemicals by enzymes is assumed to be a saturable process using Michaelis-Menton kinetics that was determined through *in vitro* studies (Gearhart and other, 1994). It is also assumed that the release of acetylcholine and diffusion across the synaptic cleft occurs instantaneously. Additionally, it is assumed that organophosphate-oxime complexes behave the same as organophosphate molecules, thus can be lumped together as a single entity within the model.

Parameters and Coefficients

The parameters and coefficients used in the model were based on literature values or the model was used to fit the parameters to reproduce literature values. Many of the values for the coefficients and parameters were retained from the values used in Seaman's model. A full list of the parameters and coefficients used within the model can be found in Appendix B.

The metabolic coefficients for atropine and oxime were determined from fitting the model to the half-life values and amount excreted in the urine that was cited in literature observations (Meridian Medical Technologies, 2007). These values varied from the values used by Seaman as the values used in his research did not mimic the data found in literature. Additionally, values for the kinetic rate constants of the organophosphate used were mainly based on the values by Seaman with a few exceptions. The rate of inhibition was adjusted for BuChE to occur at a lower rate than AChE as literature values indicated that for very strong organophosphates such as VX, the inhibition of AChE can be up to two to three times as high as that for BuChE (Worek, 2004). To determine the symptom curve values in the model for when symptoms and death occurs, the value of the symptom curve was observed for the levels cited by Ashani and Pistinner. Ashani and Pistinner suggest that symptoms occur when acetylcholinesterase levels in the tissues drop below 35% of basal levels and that a level of 10% of basal levels is required to sustain critical brain and diaphragm functions (Ashani and Pistinner, 2004). At an inhibition of acetylcholinesterase levels to 35% of basal levels, a symptom level of 1.48 was observed. At a level of 10% of basal levels, a symptom level of 1.90 was observed. Based on these observations, it was assumed in all

simulations that symptoms began to occur with a symptom level of 1.48 and death occurs when the symptom level reaches 1.90. The symptom curve has a value of 1.00 when no exposure to organophosphate or treatment with atropine has occurred. When atropine is introduced into the system without an organophosphate exposure, the symptom curve levels drop below 1.00. Literature suggests that atropine doses of 10 mg produce adverse effects in patients that have not been exposed to organophosphates (USARMICD 2007). To determine the symptom curve level associated with an adverse reaction from a dose of atropine, 10 mg of atropine was introduced to the model. The symptom curve level dropped to a minimum value of 0.35. For model simulations, a value of 0.35 was assumed to indicate adverse effects in the patient from overtreatment with atropine.

The method used to determine the overall effectiveness of the treatment administered was the area under the symptom curve. This method will account for duration and intensity of symptoms. The area under the symptom curve was normalized by dividing the area under the symptom curve from a specific treatment by the area under the symptom curve without exposure or treatment. Additionally, the minimum and maximum symptom curve levels were observed to determine the performance of a specific treatment.

Simulation Protocol

The simulations were broken down into three sets, a set for intramuscular antidote administration, a set for intravenous antidote administration, and finally, a set for analyzing the current antidote treatment guidelines. A full list of the simulation protocols can be found in Appendix C. Each set was compared to a set of nine simulations with

varying organophosphate exposures, but without antidote treatment. The nine simulations were composed of a combination of organophosphate exposures that lasted 5, 15, and 30 minutes and caused mild, severe, or lethal symptoms. For each simulation, the time that symptoms appeared, duration of symptoms, time of death, maximum symptom level, minimum symptom level, and total area under the symptom curve were recorded.

The first set of simulations consisted of administering atropine and pralidoxime intramuscularly. For each dose of antidote, the same nine simulations of varying organophosphate exposure were used. This set of intramuscular antidote administration was further broken down into 27 simulations of atropine treatment only, 27 simulations of pralidoxime only, and 81 simulations using both atropine and pralidoxime. Atropine doses were 2 mg each and up to three doses were injected at times of 2, 17, and 32 minutes after symptoms first appear. The strategy was similar for pralidoxime treatment with the exception of a 600 mg dose, rather than 2 mg.

The second set of simulations looked at administering atropine and pralidoxime intravenously. The quantity for each dose was the same as the quantity used for administering intramuscularly, with the exception of the administering of the intravenous dose slowly over a period of time. The timing varied with treatment being delayed to simulate the time required for the arrival of first responders or for the patient to arrive at the emergency room. Atropine was administered up to three times at 15, 30, and 45 minutes following the first appearance of symptoms, while pralidoxime was administered at 15, 45, and 75 minutes following the first appearance of symptoms. Pralidoxime was administered slowly over a period of 20 minutes.

Additionally, a set of simulations were run using the current recommendations established by the CDC, NYDH, and USAMRICD. Each set of recommendations was run against each of the nine exposure scenarios. These simulations helped determine the effectiveness or ineffectiveness of the current recommendations available to first responders and physicians.

The results of these simulations provided vital information that will indicate which therapeutic dosing strategies are the most effective at reducing symptoms, preventing death, as well as reducing the period of time that the patient experiences symptoms. The treatment protocols were sorted and ranked based on their ability to reduce the severity of symptoms (intensity and duration), death, and their ability to move the patient towards recovery. Based on the results of these preliminary simulations, additional simulations were performed to optimize the treatment guidelines.

IV. Results and Analysis

Intramuscular treatment series

A detailed list of results for each exposure level and type of treatment along with the simulation protocols can be found in Appendix D. The exposure concentrations for each of the three mild exposure durations varied in order to produce similar symptom levels across the set of mild exposures. These different exposure durations were implemented to determine if exposure duration had an effect on treatment and treatment simulations were compared with a specific exposure only and not across all mild exposures. This procedure was also used for the severe and lethal exposure sets. The three different mild exposures all produced symptoms at approximately the same time in the model. For the mild exposures, symptoms first appear from 81 to 85 minutes after exposure. Additionally, the maximum symptom level ranged from1.66 to 1.73 and the normalized area under the symptom curve ranged from 1.42 to 1.43.

All treatment scenarios involving atropine provided a benefit as compared to the organophosphate exposure alone to include all of the established treatment protocols. Conversely, oxime treatment alone without atropine treatment produced more harmful effects than the organophosphate exposure alone. In all exposure scenarios and in each of the three oxime treatments without atropine, an increase in the maximum symptom level and area under the symptom curve occurred. Additionally, a simulation involving the 30-minute mild exposure with a single oxime dose of 600 mg treatment produced a maximum symptom level of 1.86 as compared to 1.73 without treatment. A symptom value of 1.86 also brought the patient close to the 1.90 symptom value for death.

The harmful effects of oxime treatment were also evident in treatments involving atropine. While these treatments performed better than with no treatment administered, treatment with atropine alone performed better than a treatment with atropine and oxime. Simulations involving three different dosing strategies of atropine alone were compared with the same atropine dosing strategy with oxime treatment. In each case, the atropine treatment alone resulted in a lower maximum symptom level and a smaller area under the symptom curve. As shown in Figure 2, the symptom curve is elevated following the injection of the oxime dose as compared to treatment with atropine alone. To further analyze this observation, the treatment scenario that performed the best with respect to area under the symptom curve was compared to an additional simulation performed with the same atropine dosing strategy, but without the oxime treatment. As seen with the other simulations, the additional simulation without oxime treatment performed better than the same atropine treatment with oxime administered. In fact, this additional simulation with atropine alone was the best performer of all the treatment scenarios for this particular exposure. The model confirms that oxime treatment administered at the same time as atropine provides no benefit for mild exposures.

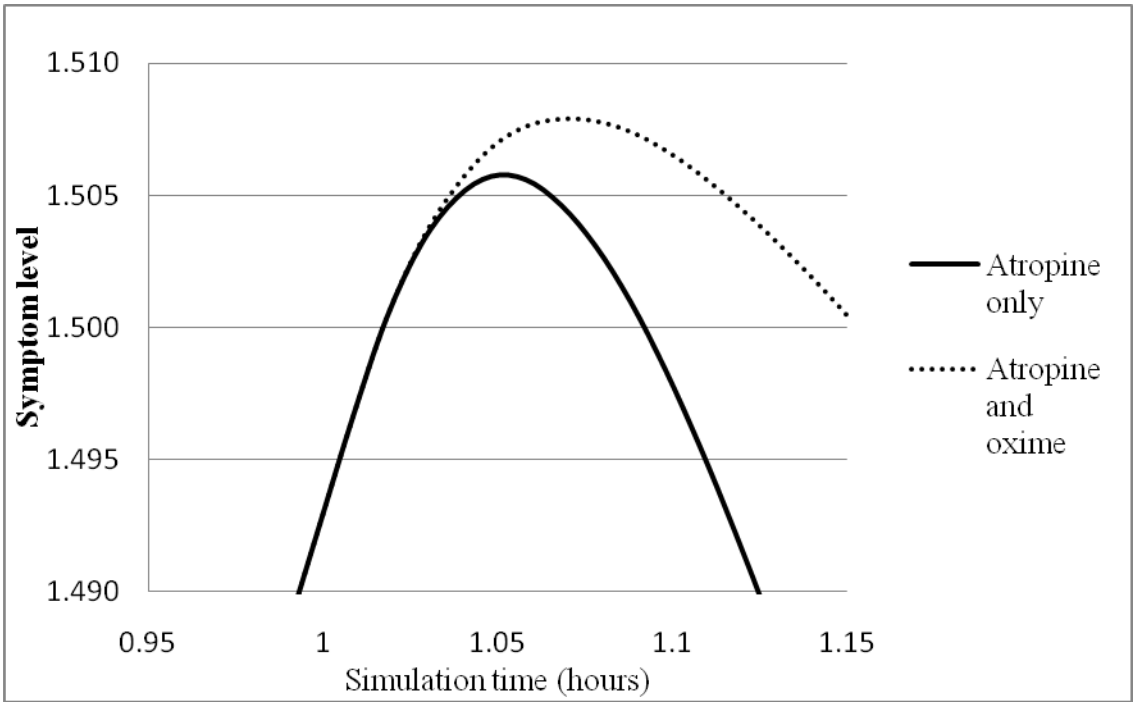

Figure 2 - Effect of oxime use on symptom level

To determine if an alternate treatment method would enable the use of oxime treatment without having an increase in severity of symptoms at the point of injection, a simulation with an oxime injection delayed 10 minutes following the first atropine treatment was performed. Small doses of oxime, such as 600 mg, caused the overall area under the symptom curve to increase and also caused symptoms to be prolonged. A second simulation using 2000 mg produced a lower area under the symptom curve, but as with the first simulation, symptoms occurred for a longer period of time. Additionally, shortly following the injection of oxime, the symptom level had a second peak that was higher than the first peak before atropine began to reduce symptoms. A 10-minute delay in administering oxime did not prevent the symptom level from peaking higher than treatment without oxime. An additional simulation delaying the 2000 mg injection of oxime until 20 minutes had passed from the start of atropine treatment proved to provide

a reduction in area under the symptom curve without having a symptom level increase above atropine treatment alone. Symptoms occurred with this treatment for 10 minutes longer than with atropine treatment alone. The benefits of the delayed oxime treatment can be seen with the levels of acetylcholinesterase at the end of simulation. With atropine treatment alone, acetylcholinesterase levels were 43.5% of basal levels, while levels were at 62.5% of basal levels with the oxime treatment.

Optimization of atropine treatment was required as increasing doses of atropine produced better results with respect to the area under the symptom curve. As a safeguard against an atropine treatment being administered to a patient that had not been exposed to an organophosphate, only individual doses of atropine smaller than 10 mg were investigated. Evaluation of increasing atropine dosing of 1 mg between simulations revealed that increasing dosage provided an added benefit. Each additional milligram of atropine provided a diminishing benefit. To determine the optimal dosage, the additional dosage of atropine as a percentage of the previous simulation was compared to the additional benefit provided to the area under the symptom curve. As an example, increasing the dosage from 1 to 2 mg, a 100% increase in dose, reduced the area under the curve from 1.3552 to 1.3195, a 2.64% decrease. This produced a ratio between the two percentages of 0.0264. A lower value reflects less additional benefit for a particular dose increase than a higher value would have. This value continues to increase for each subsequent increase of atropine up to 5 mg, after which, this ratio begins to decrease, indicating that approximately 5 mg of atropine is an optimal dose for this particular exposure. This ratio with respect to atropine dose is shown in Figure 3. This method

produced similar results for each of the three mild exposures, with 5 mg of atropine proving to be the optimal initial dose of atropine for mild exposures.

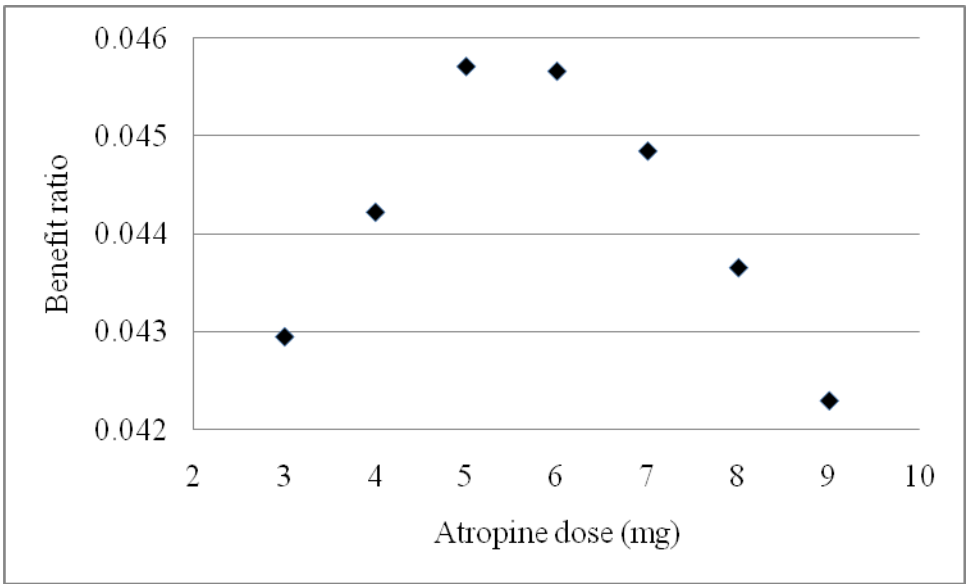

Figure 3 - Benefit of initial dose quantity of atropine

The next step in the optimization process involved the repeated doses of atropine and the subsequent timing. As may be expected, as time between the initial dose and the second dose increased, the overall effectiveness of the treatment decreased. The optimal timing of a repeat dose would be as soon as possible following the previous dose. Ideally, this time between doses should be long enough to determine if the previous dose was sufficient to treat the patient. For all mild exposures, the initial dose of 5 mg reduced patients below a symptomatic level fairly rapidly. Based on these findings, a repeat dose 10 minutes following the preceding dose would likely provide optimal benefits as well as provide enough time between doses to evaluate the patient's condition.

The final step in determining the optimal treatment was to determine the optimal dose of the repeat doses. As with the initial dose, increasing the dosage of the second dose increased the benefit to the patient with respect to the area under the symptom

curve. Additionally, there was no change observed in the maximum symptom level. The initial atropine treatment caused the symptom curve to decline from the point of injection and all subsequent doses were injected at a lower symptom level than that at the time of the first injection. For the quantity of the repeat doses, the additional benefit of the atropine decreased with an increasing quantity of atropine per dose. Therefore, a 1 mg dose was selected for repeat doses. The performance of this guideline to treat an exposure that produces mild symptoms is shown in Figure 4.

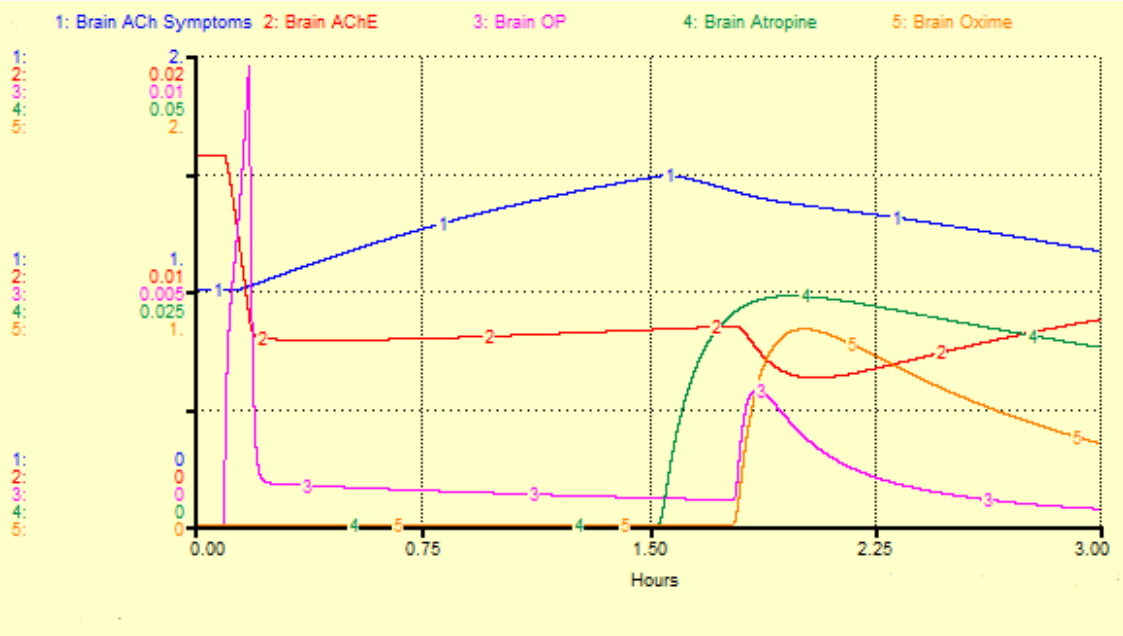

Figure 4 - Exposure causing mild symptoms with one atropine dose (5 mg) and a delayed dose of oxime (1000 mg)

The three different severe exposures all produced symptoms and death at approximately the same time in the model. The time when symptoms first appear ranged from 53 to 66 minutes following exposure and the occurrence of the death ranged from 166 to 174 minutes following exposure. Additionally, the maximum symptom level ranged from 1.90 to 1.91 and the normalized area under the symptom curve ranged from 1.53 to 1.58.

As was seen with the simulations performed with a mild exposure, oxime treatment appeared to cause more harm than treatment with atropine alone. To further illustrate this, the top ranked simulation based on area under the symptom curve was performed under the same conditions, but without oxime treatment. The simulation with only atropine treatment proved to produce a lower maximum symptom level as well as a lower area under the symptom curve. Although, delaying the oxime treatment for 20 minutes after the initial atropine injected increased acetylcholinesterase activity and did not increase the maximum symptom level.

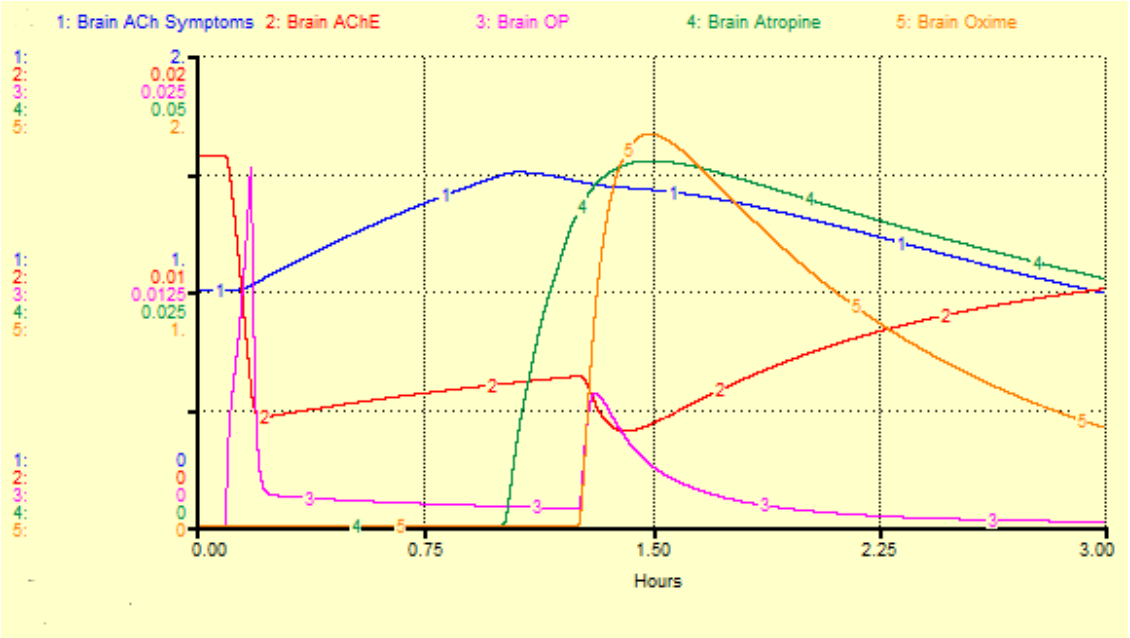

Figure 5 - Exposure causing severe symptoms with three atropine doses (one 6 mg dose and two 1 mg doses) and a delayed dose of oxime (2000 mg)

Optimization of the atropine treatment was performed for this set of exposures as had been performed on the mild symptom group. As the dose of atropine increased, the level of symptoms continued to decrease. Determining the optimal dose was required and the method used for mild symptoms was employed. It was determined that 6 mg of atropine was the optimal dose for the initial dose of atropine. Additionally, a repeat dose

of 1 mg was determined to be optimal at decreasing symptoms. The sooner the repeated dose was administered, the quicker that the patient stopped experiencing symptoms. A time period of 10 minutes was assumed to be an adequate time between injections to reassess the patient to determine if atropine treatment should continue. This treatment recommendation was simulated with an exposure that produces severe symptoms and is shown in Figure 5.

The three different lethal exposures all produced symptoms and death at approximately the same time in the model. The time that symptoms first appeared ranged from 36 to 44 minutes and the time that death occurred ranged from 82 to 85 minutes after exposure. Additionally, the maximum symptom level ranged from 2.20 to 2.27 and the normalized area under the symptom curve ranged from 1.78 to 1.79.

When comparing the treatment scenarios involving atropine alone against atropine with oxime, a noticeable difference occurred that had not been noted in the mild and severe scenarios. While the simulations involving just atropine proved to cause a lower maximum symptom level as compared to the same atropine treatment along with oxime, the area under the symptom curve was lower with the oxime treatment. This difference appears to occur due to how the simulations were performed. Since treatment begins after the first sign of symptoms (1.48 on the symptom curve), treatment occurs sooner with the higher exposures in the lethal exposure group. Additionally, oxime treatment does provide a benefit of reducing the severity of symptoms more rapidly over atropine treatment alone. Despite this benefit, in every simulation performed to compare the benefits of oxime treatment to no oxime treatment, the simulations with oxime

treatment always had a higher maximum symptom level than the simulation without oxime treatment.

As with other levels of organophosphate exposure, increasing quantities of atropine treatment produced better results in a patient. Therefore, optimization of atropine treatment was required. As was seen in previous simulations, each additional of 1 mg of atropine in an initial dose provided additional protection against organophosphate poisoning, but with each additional milligram of atropine provided a diminishing benefit. To determine the optimal dosage, the additional dosage of atropine as a percentage of the previous simulation was compared to the additional benefit provided to the area under the symptom curve. Using the same method of optimizing the atropine dose revealed an optimal dose of 6 mg. This method produced similar results for each of the three lethal exposures, and 6 mg of atropine was determined to be the optimal initial dose for lethal exposures.

With the optimal initial dose determined, the optimization of repeat doses was performed. As seen in other simulated exposure scenarios, a patient's symptoms improve sooner when a repeated dose is administered soon after the previous dose. With the same reasoning as before and for a simpler set of recommendations, a 10-minute time interval between doses was chosen for severe symptoms.

The final step in determining the optimal treatment was to determine the optimal dose of the repeat doses. As with the initial dose, increasing the second dose increased the benefit to the patient with respect to the area under the symptom curve. Additionally, there was no change observed in the maximum symptom level. The optimal dose determined for the repeat dose of atropine was 1 mg. To evaluate this treatment method

to determine if a 1 mg dose is an optimal dose, additional simulations were performed. A simulation was performed to determine the number of 1 mg doses that would be required to reduce the symptoms below 1.48 on the symptom curve. The simulation determined that eight doses (8 mg) were required. Repeating this method using 2 mg doses resulted in seven doses (14 mg) of atropine being required to reduce the symptom level below 1.48. This verified that the 1 mg dose for a repeat dose was more optimal than a 2 mg dose due to requiring a smaller quantity of atropine to alleviate symptoms in the patient. To verify this treatment guideline, a simulation was performed with a lethal dose of organophosphate and the results of the treatment are shown in Figure 6. In this scenario, atropine treatment began with a 7 mg dose 2 minutes after the symptom curve reached 1.48 and continued with 1 mg repeat doses at 10 minute intervals until symptoms dropped below 1.48. Oxime treatment began with a 2000 mg dose 20 minutes after the first atropine dose. The symptom level continued to drop following the cessation of treatment and stabilized at a level well below symptom levels, but above levels that would cause adverse effects due to atropine toxicity.

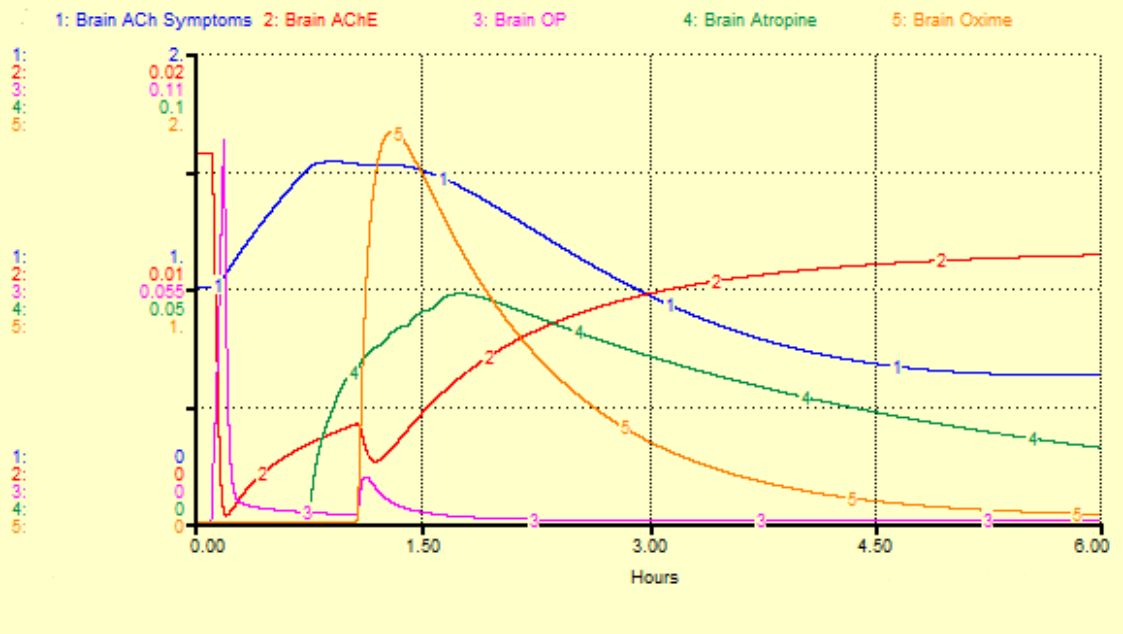

Figure 6 - Exposure causing severe symptoms with three atropine doses (one 6 mg dose and eight 1 mg doses) and a delayed dose of oxime (2000 mg)

A potential issue involved with a delayed oxime treatment is significant aging will occur with organophosphates that age more quickly, such as soman. To illustrate this in the model, the organophosphate in the model was adjusted to age more quickly with acetylcholinesterase and butyrylcholinesterase; carboxylesterase does not age with the organophosphate in the model. The oxime treatment with this organophosphate made the acetylcholinesterase levels lower at the end of the simulation as compared to levels with atropine treatment alone. This can be partly explained by the oxime freeing the organophosphate molecules that were bound to the carboxylesterase and were then available to bind with acetylcholinesterase. Therefore, the use of oxime treatment proves to be beneficial with organophosphates that do not age quickly, such as pesticides.

Intravenous treatment series

The organophosphate exposures for the intravenous treatment series are the same as the exposures used for the intramuscular treatment series. The treatment for this series is introduced intravenously and is represented in the model with an input directly into the venous tissue compartment. In theory, this should distribute the antidotes more quickly and efficiently than an intramuscular injection. The same method to determine the optimal dose of atropine was used for intravenous treatment as was used for intramuscular treatment. The difference between the two treatment methods is that the intravenous method was administered slowly over a 10-minute period beginning 15 minutes after symptoms present compared to a single injection 2 minutes after symptoms present. The optimal dose of atropine for a mild exposure proved to be 4 mg over the 10-minute period. This amount can also be expressed as 0.4 mg/min or 24 mg/hr. At the end of the 10-minute interval, a 5-minute period with the IV line turned off was assumed to be an adequate time period to reassess the patient's symptoms. If symptoms persist, additional doses should be administered. The same rate of administering atropine should be repeated over additional 10-minute intervals until symptoms of organophosphate poisoning disappear.

The procedure was repeated for the severe exposure scenarios and a dose of 6 mg of atropine slowly over 10 minutes was determined to be the optimal dose for this exposure. This corresponds to a rate of administration of 0.6 mg/min or 36 mg/hr. As with treatment for mild exposures, this rate should be repeated over 10-minute intervals with a 5-minute period between doses to assess the patient's symptoms. Treatment should continue until the symptoms of organophosphate poisoning cease.

Finally, evaluation of the optimal IV dose of atropine for the lethal exposure set was performed. A dose slightly higher than for the severe exposures, 7 mg over 10 minutes, was deemed to be the optimal dose. This corresponds to a rate of 0.7 mg/min or 42 mg/hr. The procedure for repeated doses is the same as was described for mild symptoms with 10 minutes of treatment followed by a 5-minute assessment period. Treatment should continue until symptoms are no longer present. The performance of this treatment protocol for intravenous introduction of antidotes was evaluated in the model and the results are shown in Figure 7. In this scenario, atropine treatment began 15 minutes following the presentation of symptoms with oxime treatment following 20 minutes after the start of atropine treatment. The exposure required two full 10-minute treatments minutes and the third interval being turned off once symptom levels dropped below 1.48. Symptom levels stabilized below the level required for symptoms to appear in the patient at a time period 6 hours following exposure.

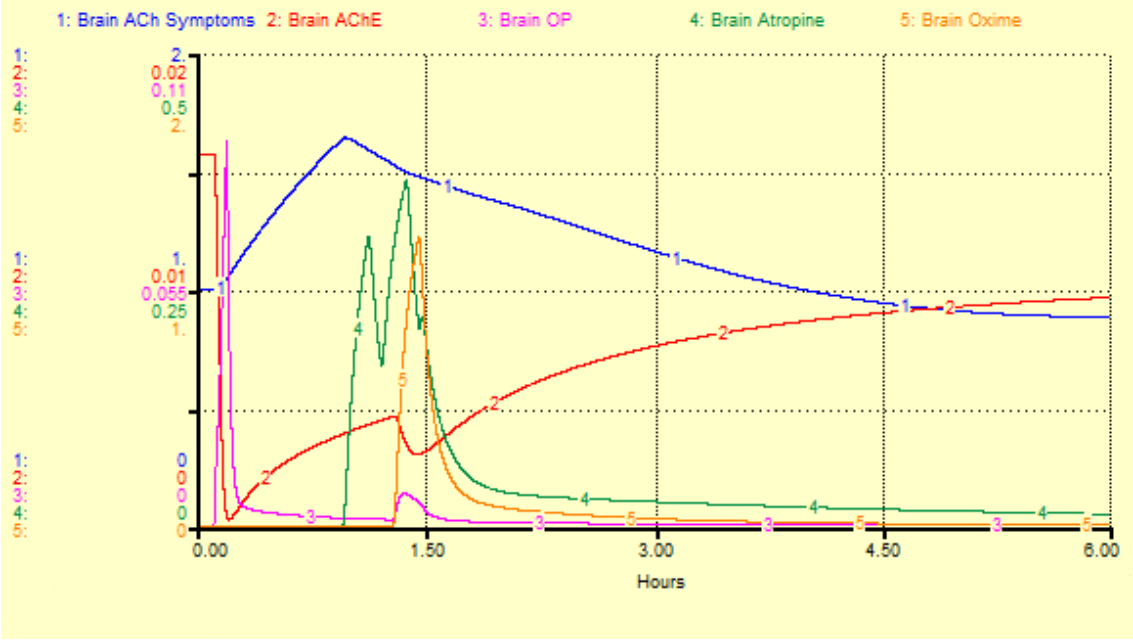

Figure 7 - Exposure causing severe symptoms with IV treatment of atropine and a delayed dose of oxime (2000 mg)

With the atropine treatment optimization complete, an evaluation of another potential treatment scenario that could take advantage of the beneficial properties of oxime was performed by delaying the oxime treatment by 15 minutes following the treatment with atropine. This method showed promise as it would allow atropine to fully circulate the system and begin lowering the symptom level prior to the spike seen with oxime treatment in other scenarios. A 5-minute lethal exposure was treated with the optimal dosing strategy developed earlier and the time symptoms ended, 1.387 hours from the beginning of the simulation, and the normalized area under the symptom curve, 1.31, were noted. The second simulation treated the patient with 600 mg of oxime slowly over a 20-minute period. The oxime treatment was not introduced until 15 minutes following the beginning of atropine treatment. With this treatment, symptoms occurred until 1.481 hours following the start of the simulation and a normalized area under the symptom curve of 1.33; thus, both metrics proved to be worse than with the atropine

treatment alone. A higher dose of oxime administered over a shorter time period proved to be more effective. A 2000 mg oxime dose over 10 minutes reduced the normalized area under the symptom curve to 3.77 while not increasing the maximum symptom level seen with atropine treatment alone. Symptoms do occur for a longer period of time under this treatment scenario, lasting until 1.437 hours after the beginning of the simulation.

Although it appears that this treatment protocol with oxime would be a successful method of taking advantage of the beneficial properties of oximes, a closer look at whether this trend would continue with an organophosphate that ages more quickly is warranted. As was done with the intramuscular series, an organophosphate that ages more quickly was introduced into the model and the same treatment guidelines were administered. Results similar to those found during the intramuscular series occurred with the intravenous treatment. Acetylcholinesterase levels, total area under the symptom curve, and the symptom level at the end of the simulation were all worse than with atropine treatment alone. Delaying oxime treatment has several risks involved. First, the longer duration between exposure to the organophosphate and the first treatment of oxime is long enough to allow significant aging to occur with strong organophosphates such as nerve agents. Second, organophosphates that have not aged are released to bind with all available esterase.

V. Discussion

Research Objectives

1. Validate the physiologically-based pharmacokinetic (PBPK) model produced by Seaman and modify it as necessary to perform the simulations required to complete this research

The model developed by Seaman was thoroughly analyzed and modified as needed prior to any simulations performed for this research. The modifications performed on the model included both functional and aesthetic changes. In order to evaluate intravenous treatment methods during this research, inputs were added for atropine and oxime that introduced a quantity of these antidotes directly to the venous compartment. The model developed by Seaman used unconventional parameters that are not typically seen in PBPK modeling. Specifically, the model included "normalization factors" for each tissue type that described the volume of a specific tissue with respect to total body weight. The normalization factors were replaced in favor of tissue volume parameters to conform to a traditional PBPK model format. A tissue concentration for each component was added using the mass of the particular component in that tissue and the tissue volume. Additionally, in kinetic equations, the use of mass in the equations was eliminated in favor of tissue volume and concentration. This format is more consistent with traditional PBPK models and mass balance equations involving kinetics. The final functional modification to the model was the adjustment of the metabolic rates of degradation of atropine and oxime. The metabolic parameters were adjusted to fit to the data for a DuoDote autoinjector that contains both atropine and pralidoxime (Meridian Medical Technologies, 2007).

2. Analyze the current therapeutic strategies using the validated PBPK model in various exposure situations to determine if they are effective or cause harm

The treatment guidance developed by the CDC, NYDH, USAMRICD, and WHO was analyzed with the model for a variety of scenarios. Based on the simulation results, all of the treatment scenarios improved the patient's health as opposed to not receiving any treatment at all. Despite this fact, none of the guidance that was examined during this research was the optimal use of the antidotes available. The use of oximes in any particular treatment scenario caused a momentary spike in maximum symptoms as compared to treating with atropine alone. This is important to note as that spike in symptoms may be the difference in the patient dying or surviving. The benefits of oxime use are clearly seen in the simulation results as well. Oxime treatment increases the concentration of available acetylcholinesterase in the body to break down acetylcholine and causes the symptom curve to decline at a faster rate than with atropine treatment alone.

The use of oxime to treat organophosphate poisoning has significant risks and benefits that need to be carefully examined before treatment with oxime is advised. The risk of the patient dying as a result of receiving a treatment including oxime clearly increases as the symptoms of the patient are more severe. Therefore, medical personnel should reconsider treating patients with oximes for severe organophosphate poisoning. Unfortunately, patients with severe exposures are in the most need of the beneficial properties of oxime treatment.

Conversely, the use of oximes while treating a patient with mild symptoms is not likely to cause a large enough increase in severity of symptoms to cause death. Even without oxime treatment, a patient with a mild exposure will have a sufficient quantity of unbound acetylcholinesterase available to sustain primary life functions, and the model suggests that atropine treatment alone is effective in alleviating the symptoms a patient may be experiencing. Based on the data from the simulations performed with simultaneous introduction of atropine and oxime, oxime treatment either posed a significant risk of causing harm (severe exposures) or had limited effectiveness over atropine treatment alone (mild exposures). Delaying the oxime treatment until after atropine treatment has begun appears to provide beneficial results for relatively weak organophosphates. Neither initial dosing with atropine and oxime, nor delaying oxime treatment for strong organophosphates was beneficial for the patient Consequently, an optimized treatment strategy of initially treating with atropine alone followed by a delayed treatment with oxime was developed only for weak organophosphates such as pesticides while another strategy was developed for strong organophosphates such as nerve agents, involving only atropine.

3. Develop a set of guidelines that provides an optimal dosing and timing strategy for various exposure situations to include military, terrorist, or occupational exposures to reduce death among initial survivors and hasten full recovery.

The potential of oximes to cause harm was clearly evident in the results of this research. Due to their potential to cause the symptoms of a patient to worsen or even

cause death, the guidelines developed here do not recommend their use as recommended by current guidelines. In order to receive the beneficial effects of oxime treatment without the spike in symptoms that occurs upon injection, oxime treatment must be delayed to a point after atropine treatment has begun. Consequently, atropine treatment is advised immediately followed by a delayed treatment with oximes. With the use of the model, an optimal dose of atropine was examined for an initial dose, repeat doses, and the subsequent timing between these doses. This optimization was performed for varying levels of organophosphate exposure to determine if the quantity of organophosphate present affects the optimal atropine dosing required.

Recommendations

The primary goal of this research was to develop a set of treatment guidelines for organophosphate poisoning based on simulations performed with a PBPK model. The guidelines are presented in the following four tables, two for exposure to weak organophosphates and two for exposure to strong organophosphates or if the type of organophosphate is unknown. Tables 3 and 4 are designed to treat exposures to weak organophosphates and have separate guidelines based on the severity of the symptoms. If any severe symptoms are present, the medical provider should use the set of guidelines for severe symptoms. The symptoms are based on the CDC definition of mild to moderate symptoms that include localized sweating, muscle twitching, nausea, vomiting, muscle weakness, and dyspnea and severe symptoms that include unconsciousness, convulsions, apnea, and paralysis (CDC, 2010). If intravenous treatment is available, this method should be used to begin treating the patient. Intramuscular treatment would

ideally be used in the field outside of a medical treatment facility when the only method of treatment available is autoinjectors.

Table 3. Intramuscular treatment for weak organophosphates (pesticides)

		Mild/Moderate Symptoms	Severe Symptoms
Atropine	Initial Dose	5 mg	6 mg
	Repeat Dose	1 mg	1 mg
	Repeat Interval until symptoms are no longer present	10 min	10 min
Pralidoxime	Initial Dose	1000 mg	2000 mg
	Timing	20 min after first atropine treatment	20 min after first atropine treatment
	Repeat dose	None	None

Table 4. Intravenous treatment for weak organophosphates (pesticides)

		Mild/Moderate Symptoms	Severe Symptoms
Atropine	Initial dose	0.4 mg/min for 10 min	0.7 mg/min for 10 min
	Repeat dose	0.4 mg/min for 10 min	0.7 mg/min for 10 min
	Repeat interval until symptoms are no longer present	5 min	5 min
Pralidoxime	Initial dose	100 mg/min for 10 min	200 mg/min for 10 min
	Timing	20 min after first atropine treatment	20 min after first atropine treatment
	Repeat dose	None	None

Tables 5 and 6 are designed to treat exposures to strong organophosphate or if the type of organophosphate exposed to is unknown. These two tables also include separate guidance for the degree of symptoms that the patient is experiencing. The notable difference between the two treatment guidelines is that oximes are not recommended treatment for exposure to strong organophosphates. If the type of organophosphate is

unknown, medical treatment should defer to the set of guidelines for treating nerve agents. It should be noted that the same atropine treatment is used regardless of the type of organophosphate exposed to. If symptoms reappear after treatment has ceased, treatment should continue where left off with continuing treatment with the repeat dosing presented in the tables. Additionally, if the intravenous treatment becomes available subsequent to intramuscular treatment, treatment should transition to intravenous treatment.

Table 5. Intramuscular treatment for strong organophosphates (nerve agents)

		Mild/Moderate Symptoms	Severe Symptoms
Atropine	Initial Dose	5 mg	6 mg
	Repeat Dose	1 mg	1 mg
	Repeat Interval until symptoms are no longer present	10 min	10 min
Pralidoxime	Initial Dose	None	None

Table 6. Intravenous treatment for strong organophosphates (nerve agents)

		Mild/Moderate Symptoms	Severe Symptoms
Atropine	Initial dose	0.4 mg/min for 10 min	0.7 mg/min for 10 min
	Repeat dose	0.4 mg/min for 10 min	0.7 mg/min for 10 min
	Repeat interval until symptoms are no longer present	5 min	5 min
Pralidoxime	Initial dose	None	None

For deployed military members in the field, Table 5 would be the only table used. This is significant since military members are currently issued auto-injectors with both antidotes and Table 5 does not recommend oxime use. The guidelines for military

members in the field pose a significant risk and may cause symptoms of exposed personnel to worsen following treatment.

These guidelines are based on the patient being an adult male of average size. Additional research and simulations would be required to develop a set of guidelines for children, the elderly, and females due to physiological differences such as body composition and weight. Other potential antidotes such as butyrylcholinesterase would require minor model modifications to determine if they would improve the survival and aid in reducing symptoms.

Appendix A – Equations

Organophosphates

Slowly Perfused, Thigh, Diaphragm, and Fat Tissues

$$V_T \frac{dC}{dt} = F_T Q_C \left(C_A - \frac{C_T}{P}\right)$$

Brain, Liver, Kidney, and Richly Perfused Tissues

$$V_T \frac{dC}{dt} = F_T Q_C C_A - \frac{F_T Q_C C_T}{P} - \frac{V_{max} C_T}{K_m + C_T}$$

Venous Tissue

$$V_V \frac{dC}{dt} = Q_C \sum F_T C_T - Q_C C_V - \frac{V_{max} C_V}{K_m + C_V}$$

Lung Tissue

$$Q_P C_{air} + Q_C C_V = \frac{Q_P C_A}{P} + Q_C C_A$$

Arterial Tissue

$$V_A \frac{dC}{dt} = Q_C C_L - Q_C C_A - \frac{V_{max} C_A}{K_m + C_A}$$

Oxime

Brain, Diaphragm, Fat, Richly Perfused, Slowly Perfused Tissues

$$V_T \frac{dC}{dt} = F_T Q_C \left(C_A - \frac{C_T}{P}\right)$$

Kidney Tissue

$$V_T \frac{dC}{dt} = F_T Q_C \left(C_A - \frac{C_T}{P} - E C_A\right)$$

Liver Tissue

$$V_T \frac{dC}{dt} = F_T Q_C C_A - \frac{F_T Q_C C_T}{P} - \frac{V_{max} C_T}{K_m + C_T}$$

Thigh Tissue

$$V_T \frac{dC}{dt} = F_T Q_C C_A + IM - \frac{F_T Q_C C_T}{P}$$

Venous Tissue

$$V_V \frac{dC}{dt} = Q_C \sum F_T C_T + IV - Q_C C_V$$

Arterial Tissue

$$V_A \frac{dC}{dt} = Q_C (C_V - C_A)$$

Atropine

Brain, Diaphragm, Fat, Richly Perfused, Slowly Perfused Tissues

$$V_T \frac{dC}{dt} = F_T Q_C \left(C_A - \frac{C_T}{P}\right)$$

Kidney Tissue

$$V_T \frac{dC}{dt} = F_T Q_C \left(C_A - \frac{C_T}{P} - E C_A \right)$$

Liver Tissue

$$V_T \frac{dC}{dt} = F_T Q_C C_A - \frac{F_T Q_C C_T}{P} - \frac{V_{max} C_T}{K_m + C_T}$$

Thigh Tissue

$$V_T \frac{dC}{dt} = F_T Q_C C_A + IM - \frac{F_T Q_C C_T}{P}$$

Venous Tissue

$$V_V \frac{dC}{dt} = Q_C \sum F_T C_T + IV - Q_C C_V$$

Arterial Tissue

$$V_A \frac{dC}{dt} = Q_C (C_V - C_A)$$

Acetylcholinesterase

Brain, Kidney, Diaphragm, Liver, Slowly Perfused, Richly Perfused, and Thigh Tissues

$$V_T \frac{dC}{dt} = X_1 - X_2 C_T V_T$$

Butyrylcholinesterase

Brain, Kidney, Diaphragm, Liver, Slowly Perfused, Richly Perfused, and Thigh Tissues

$$V_T \frac{dC}{dt} = Y_1 - Y_2 C_T V_T$$

Carboxylesterase

Brain, Kidney, Diaphragm, Liver, Slowly Perfused, Richly Perfused, and Thigh Tissues

$$V_T \frac{dC}{dt} = Z_1 - Z_2 C_T V_T$$

Acetylcholinesterase and Organophosphate Chemical Reaction

$$\frac{d[AChE]}{dt} = k_i[AChE][OP] - k_s[AChE/OP] - k_a[AChE/OP]$$

Butyrylcholinesterase and Organophosphate Chemical Reaction

$$\frac{d[BuChE]}{dt} = k_i[BuChE][OP] - k_s[BuChE/OP] - k_a[BuChE/OP]$$

Carboxylesterase and Organophosphate Chemical Reaction

$$\frac{d[CaE]}{dt} = k_i[CaE][OP] - k_s[CaE/OP] - k_a[CaE/OP]$$

Oxime and Acetylcholinesterase-organophosphate complex chemical reaction

$$\frac{d[AChE/OP]}{dt} = k_r[AChE/OP][Oxime]$$

Oxime and Butyrylcholinesterase-organophosphate complex chemical reaction

$$\frac{d[BuChE/OP]}{dt} = k_r[BuChE/OP][Oxime]$$

Oxime and Carboxylesterase-organophosphate complex chemical reaction

$$\frac{d[CaE/OP]}{dt} = k_r[CaE/OP][Oxime]$$

Atropine, Acetylcholine, and Acetylcholinesterase reaction

$$\frac{d[ACh\ site]}{dt} = p_1\left\{\frac{p_1}{p_1 + [Atropine]}\right\} - p_2[AChE][ACh\ site]$$

Symptoms

$$\frac{d\ Symptoms}{dt} = \frac{[ACh\ site]}{[Basal\ ACh\ site]}$$

List of Symbols

V_T = Volume of tissue (volume)

$\frac{dC}{dt}$ = change in chemical concentration with respect to time (mass volume^{-1} time^{-1})

F_T = Fraction of blood flow that enters the tissue (unitless)

Q_C = Cardiac Output (volume / time)

C_A = Chemical concentration in arterial tissue (mass / volume)

C_T = Chemical concentration in tissue (mass / volume)

P = Tissue to blood partition coefficient (unitless)

V_{max} = Maximum metabolism rate (mass / time)

K_m = Michaelis-Menten Constant (mass / volume)

V_V = Volume of venous tissue (volume)

C_V = Chemical concentration in venous tissue (mass / volume)

Q_P = Pulmonary ventilation rate (volume / time)

C_{air} = Chemical concentration in air (mass / volume)

V_A = Volume of arterial tissue (volume)

C_L = Chemical concentration of blood from lungs (mass / volume)

E = Elimination fraction of chemical in urine (unitless)

IM = Intramuscular (IM) injection rate (mass / time)

IV = Intravenous (IV) injection rate (mass / time)

X_1 = Acetylcholinesterase synthesis rate (mass / time)

X_2 = Acetylcholinesterase degradation rate (time^{-1})

Y_1 = Butyrylcholinesterase synthesis rate (mass / time)

Y_2 = Butyrylcholinesterase degradation rate (time^{-1})

Z_1 = Carboxylesterase synthesis rate (mass / time)

Z_2 = Carboxylesterase degradation rate (time^{-1})

k_i = Organophosphate reaction rate coefficient with esterase (mol^{-1} $time^{-1}$)
k_s = Organophosphate-esterase complex natural separation reaction rate coefficient ($time^{-1}$)
k_a = Organophosphate-esterase complex aging reaction rate coefficient ($time^{-1}$)
k_r = Organophosphate-esterase complex reaction rate coefficient with oxime(mol^{-1} $time^{-1}$)
p_1 = Acetylcholine binding rate (mass / time)
p_2 = Acetylcholine degradation constant ($time^{-1}$)

Appendix B – Parameters

Physiological Parameters			
Body Weight	60.9	kg	Gearhart et. al.
Cardiac Output	302	L/hr	Gearhart et. al.
Pulmonary Rate	354	L/hr	Gearhart et. al.
Blood Flow to Tissue Fractions			
Brain	0.134		Gearhart et. al.
Diaphragm	0.006		Gearhart et. al.
Fat	0.036		Gearhart et. al.
Kidney	0.223		Gearhart et. al.
Liver	0.27		Gearhart et. al.
Richly Perfused	0.2		Gearhart et. al.
Slowly Perfused	0.1244		Gearhart et. al.
Thigh	0.0066		Gearhart et. al.
Tissue Volumes			
Arterial	1.218	L	Gearhart et. al.
Brain	1.30326	L	Gearhart et. al.
Diaphragm	0.1827	L	Gearhart et. al.
Fat	10.353	L	Gearhart et. al.
Kidney	0.26187	L	Gearhart et. al.
Liver	2.436	L	Gearhart et. al.
RPT	2.08887	L	Gearhart et. al.
SPT	31.89942	L	Gearhart et. al.
SPT Thigh	1.68084	L	Gearhart et. al.
Venous	3.4713	L	Gearhart et. al.
Organophosphate			
Molecular Weight	184	mg/mmol	Seaman
Partition Coefficents			
Tissue -Blood Partition Coefficients			
Air-Blood	12.57		Gearhart et. al.
Arterial	1		Assumed
Brain	0.67		Gearhart et. al.
Diaphragm	0.77		Gearhart et. al.
Fat	17.6		Gearhart et. al.
Kidney	1.63		Gearhart et. al.
Liver	1.53		Gearhart et. al.
RPT	0.67		Gearhart et. al.
SPT	0.77		Gearhart et. al.
SPT Thigh	0.77		Gearhart et. al.

Venous	1		Assumed
Metabolic Parameters			
Km			
Arterial	199	mg/L	Gearhart et. al.
Brain	440	mg/L	Gearhart et. al.
Kidney	134	mg/L	Gearhart et. al.
Liver	237	mg/L	Gearhart et. al.
RPT	51	mg/L	Gearhart et. al.
Venous	199	mg/L	Gearhart et. al.
Vmax			
Arterial	216	mg/hr	Gearhart et. al.
Brain	688	mg/hr	Gearhart et. al.
Kidney	5042	mg/hr	Gearhart et. al.
Liver	52474	mg/hr	Gearhart et. al.
RPT	560	mg/hr	Gearhart et. al.
Venous	616	mg/hr	Gearhart et. al.
Oxime (Pralidoxime)			
Molecular Weight	137	mg/mmol	Calculated
Partition Coefficients			
Arterial	1		Seaman
Brain	0.67		Seaman
Diaphragm	0.77		Seaman
Fat	17.6		Seaman
Kidney	1.63		Seaman
Liver	1.53		Seaman
RPT	0.67		Seaman
SPT	0.77		Seaman
SPT Thigh	0.77		Seaman
Venous	1		Seaman
Metabolic Parameters			
KM Liver	700	mg/L	Scaled from Meridian
Vmax Liver	6500	mg/hr	Scaled from Meridian
Kidney Partition Parameter			
Elimination Partition	0.35		Scaled from Meridian
Atropine			
Molecular Weight	289	mg/mmol	Calculated
Partition Coefficients			
Arterial	1		Seaman
Brain	0.67		Seaman
Diaphragm	0.77		Seaman

Fat	17.6		Seaman
Kidney	1.63		Seaman
Liver	1.53		Seaman
RPT	0.67		Seaman
SPT	2.1		Seaman
SPT Thigh	2.1		Seaman
Venous	1		Seaman
Metabolic Parameters			
KM Liver	700	mg/L	Scaled from Meridian
Vmax Liver	6500	mg/hr	Scaled from Meridian
Kidney Partition Parameter			
Elimination Partition	0.35		Scaled from Meridian
Acetylcholinesterase			
Molecular Weight	75,000	mg/mmol	Assumed
Synthesis Rate			
Arterial	0.0001	µmol/hr	Gentry et. al.
Brain	0.00002	µmol/hr	Scaled from Gentry et. al.
Diaphragm	0.000003	µmol/hr	Scaled from Gentry et. al.
Kidney	0.000004	µmol/hr	Scaled from Gentry et. al.
Liver	0.00004	µmol/hr	Scaled from Gentry et. al.
RPT	0.00003	µmol/hr	Scaled from Gentry et. al.
SPT	0.0005	µmol/hr	Scaled from Gentry et. al.
SPT Thigh	0.00002	µmol/hr	Scaled from Gentry et. al.
Venous	0.0001	µmol/hr	Gentry et. al.
Initial Concentration			
Arterial	0.001212	µmol	Gentry et. al.
Brain	0.04928	µmol	Gentry et. al.
Diaphragm	0.000909	µmol	Gentry et. al.
Kidney	0.000104	µmol	Gentry et. al.
Liver	0.002424	µmol	Gentry et. al.
RPT	0.008314	µmol	Gentry et. al.
SPT	0.222196	µmol	Gentry et. al.
SPT Thigh	0.011708	µmol	Gentry et. al.
Venous	0.003454	µmol	Gentry et. al.
Degradation Constant			
Arterial	0.082508251	hr^{-1}	Calculated
Brain	0.000405844	hr^{-1}	Calculated
Diaphragm	0.00330033	hr^{-1}	Calculated
Kidney	0.038461538	hr^{-1}	Calculated
Liver	0.01650165	hr^{-1}	Calculated

RPT	0.003603837	hr^{-1}	Calculated
SPT	0.002250266	hr^{-1}	Calculated
SPT Thigh	0.001708234	hr^{-1}	Calculated
Venous	0.02895194	hr^{-1}	Calculated
Butyrylcholinesterase			
Molecular Weight	83,000	mg/mmol	Assumed
Synthesis Rate			
Arterial	0.0001	µmol/hr	Gentry et. al.
Brain	0.00002	µmol/hr	Scaled from Gentry et. al.
Diaphragm	0.000003	µmol/hr	Scaled from Gentry et. al.
Kidney	0.000004	µmol/hr	Scaled from Gentry et. al.
Liver	0.00004	µmol/hr	Scaled from Gentry et. al.
RPT	0.00003	µmol/hr	Scaled from Gentry et. al.
SPT	0.0005	µmol/hr	Scaled from Gentry et. al.
SPT Thigh	0.00002	µmol/hr	Scaled from Gentry et. al.
Venous	0.0001	µmol/hr	Gentry et. al.
Initial Concentration			
Arterial	0.00606	µmol	Gentry et. al.
Brain	0.016859	µmol	Gentry et. al.
Diaphragm	0.002	µmol	Gentry et. al.
Kidney	0.000782	µmol	Gentry et. al.
Liver	0.019392	µmol	Gentry et. al.
RPT	0.006236	µmol	Gentry et. al.
SPT	0.190454	µmol	Gentry et. al.
SPT Thigh	0.010035	µmol	Gentry et. al.
Venous	0.017271	µmol	Gentry et. al.
Degradation Constant			
Arterial	0.01650165	hr^{-1}	Calculated
Brain	0.00118631	hr^{-1}	Calculated
Diaphragm	0.0015	hr^{-1}	Calculated
Kidney	0.00511509	hr^{-1}	Calculated
Liver	0.002062706	hr^{-1}	Calculated
RPT	0.004810776	hr^{-1}	Calculated
SPT	0.002625306	hr^{-1}	Calculated
SPT Thigh	0.001993024	hr^{-1}	Calculated
Venous	0.005790053	hr^{-1}	Calculated
Carboxylesterase			
Molecular Weight	100,000	mg/mmol	Assumed

Synthesis Rate			
Arterial	0.0001	µmol/hr	Gentry et. al.
Brain	0.00002	µmol/hr	Scaled from Gentry et. al.
Diaphragm	0.000003	µmol/hr	Scaled from Gentry et. al.
Kidney	0.000004	µmol/hr	Scaled from Gentry et. al.
Liver	0.00004	µmol/hr	Scaled from Gentry et. al.
RPT	0.00003	µmol/hr	Scaled from Gentry et. al.
SPT	0.0005	µmol/hr	Scaled from Gentry et. al.
SPT Thigh	0.00002	µmol/hr	Scaled from Gentry et. al.
Venous	0.0001	µmol/hr	Gentry et. al.
Initial Concentration			
Arterial	5.0904	µmol	Gentry et. al.
Brain	0.778104	µmol	Gentry et. al.
Diaphragm	0.52722	µmol	Gentry et. al.
Kidney	4.29957	µmol	Gentry et. al.
Liver	110.292	µmol	Gentry et. al.
RPT	442.73754	µmol	Gentry et. al.
SPT	73.007244	µmol	Gentry et. al.
SPT Thigh	3.846888	µmol	Gentry et. al.
Venous	14.50764	µmol	Gentry et. al.
Degradation Constant			
Arterial	1.96448E-05	hr^{-1}	Calculated
Brain	2.57035E-05	hr^{-1}	Calculated
Diaphragm	5.69022E-06	hr^{-1}	Calculated
Kidney	9.3032E-07	hr^{-1}	Calculated
Liver	3.6267E-07	hr^{-1}	Calculated
RPT	6.776E-08	hr^{-1}	Calculated
SPT	6.84886E-06	hr^{-1}	Calculated
SPT Thigh	0.000005199	hr^{-1}	Calculated
Venous	6.89291E-06	hr^{-1}	Calculated
Acetylcholine			
Molecular Weight	146	mg/mmol	Calculated
Activation Rate Constants			
Brain	0.00719488	mg/hr	Calculated
Diaphragm	0.000132714	mg/hr	Calculated
Kidney	0.000015184	mg/hr	Calculated
Liver	0.000353904	mg/hr	Calculated
RPT	0.001213844	mg/hr	Calculated
SPT	0.032440616	mg/hr	Calculated

SPT Thigh	0.001709368	mg/hr	Calculated
Reaction rate coefficients			
AChE			
Ka	0.1386	hr^{-1}	Assumed
Ki	220000	$mmol^{-1}$ hr^{-1}	Assumed
Kr	100	$mmol^{-1}$ hr^{-1}	Assumed
Ks	1	hr^{-1}	Assumed
BuChE			
Ka	0.054	hr^{-1}	Assumed
Ki	110000	$mmol^{-1}$ hr^{-1}	Assumed
Kr	300	$mmol^{-1}$ hr^{-1}	Assumed
Ks	1	hr^{-1}	Assumed
CaE			
Ka	0	hr^{-1}	Assumed
Ki	110000	$mmol^{-1}$ hr^{-1}	Assumed
Kr	300	$mmol^{-1}$ hr^{-1}	Assumed
Ks	1	hr^{-1}	Assumed
K Ach-AChE	20292.23826	hr^{-1}	Assumed

Appendix C – Simulation protocols

Table 7 - Intramuscular treatment protocol

	Atropine						Oxime					
	Dose 1 and timing		Dose 2 and timing		Dose 3 and timing		Dose 1 and timing		Dose 2 and timing		Dose 3 and timing	
Test	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)
1	2	2	0	0	0	0	0	0	0	0	0	0
2	2	2	2	17	0	0	0	0	0	0	0	0
3	2	2	2	17	2	32	0	0	0	0	0	0
4	0	0	0	0	0	0	600	2	0	0	0	0
5	0	0	0	0	0	0	600	2	600	17	0	0
6	0	0	0	0	0	0	600	2	600	17	600	32
7	2	2	0	0	0	0	600	2	0	0	0	0
8	2	2	2	17	0	0	600	2	0	0	0	0
9	2	2	2	17	2	32	600	2	0	0	0	0
10	2	2	2	17	0	0	600	2	600	17	0	0
11	2	2	2	17	2	32	600	2	600	17	0	0
12	2	2	2	17	2	32	600	2	600	17	600	32
13	4	2	0	0	0	0	600	2	0	0	0	0
14	6	2	0	0	0	0	1800	2	0	0	0	0
15	2	2	2	7	0	0	600	2	0	0	0	0
16	4	2	2	7	0	0	600	2	0	0	0	0
17	6	2	2	7	0	0	1800	2	0	0	0	0
18	2	2	2	7	2	12	600	2	0	0	0	0

	Atropine						Oxime					
	Dose 1 and timing		Dose 2 and timing		Dose 3 and timing		Dose 1 and timing		Dose 2 and timing		Dose 3 and timing	
Test	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)
19	4	2	2	7	2	12	600	2	0	0	0	0
20	6	2	2	7	2	12	1800	2	0	0	0	0
21	2	2	2	4	0	0	600	2	0	0	0	0
22	4	2	2	4	0	0	600	2	0	0	0	0
23	6	2	2	4	0	0	1800	2	0	0	0	0
24	2	2	2	4	2	6	600	2	0	0	0	0
25	4	2	4	4	4	6	600	2	0	0	0	0
26	6	2	6	4	6	6	1800	2	0	0	0	0
27	2	2	0	0	0	0	600	2	600	32	0	0
28	4	2	0	0	0	0	600	2	600	32	0	0
29	6	2	0	0	0	0	1800	2	1800	32	0	0
30	2	2	2	4	0	0	600	2	600	32	0	0
31	4	2	2	4	0	0	600	2	600	32	0	0
32	6	2	2	4	0	0	1800	2	1800	32	0	0
33	2	2	2	4	2	6	600	2	600	32	0	0
34	4	2	4	4	4	6	600	2	600	32	0	0
35	6	2	6	4	6	6	1800	2	1800	32	0	0
36	2	2	0	0	0	0	600	2	600	32	600	92
37	4	2	0	0	0	0	600	2	600	32	600	92
38	6	2	0	0	0	0	1800	2	1800	32	1800	92
39	2	2	2	4	0	0	600	2	600	32	600	92
40	4	2	2	4	0	0	600	2	600	32	600	92

	Atropine						Oxime					
	Dose 1 and timing		Dose 2 and timing		Dose 3 and timing		Dose 1 and timing		Dose 2 and timing		Dose 3 and timing	
Test	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)
41	6	2	2	4	0	0	1800	2	1800	32	1800	92
42	2	2	2	4	2	6	600	2	600	32	600	92
43	4	2	4	4	4	6	600	2	600	32	600	92
44	6	2	6	4	6	6	1800	2	1800	32	1800	92
45	2	2	2	12	0	0	600	2	600	12	0	0
46	2	2	2	12	2	22	600	2	600	12	600	22

Table 8 - Intramuscular treatment protocol

	Atropine						Oxime					
	Dose 1 and timing		Dose 2 and timing		Dose 3 and timing		Dose 1 and timing		Dose 2 and timing		Dose 3 and timing	
Test	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)	(mg)	(min)
47	2	15-20	0	0	0	0	0	0	0	0	0	0
48	2	15-20	2	30-35	0	0	0	0	0	0	0	0
49	2	15-20	2	30-35	2	45-50	0	0	0	0	0	0
50	0	0	0	0	0	0	600	15-45	0	0	0	0
51	0	0	0	0	0	0	600	15-45	600	45-75	0	0
52	0	0	0	0	0	0	600	15-45	600	45-75	600	75-105
53	2	15-20	0	0	0	0	600	15-45	0	0	0	0
54	2	15-20	2	30-35	0	0	600	15-45	0	0	0	0
55	2	15-20	2	30-35	2	45-50	600	15-45	0	0	0	0

	Atropine	Oxime

	Dose 1 and timing		Dose 2 and timing		Dose 3 and timing		Dose 1 and timing		Dose 2 and timing		Dose 3 and timing	
Test	**(mg)**	**(min)**	**(mg)**	**(min)**	**(mg)**	**(min)**	**(mg)**	**(min)**	**(mg)**	**(min)**	**(mg)**	**(min)**
56	2	15-20	2	30-35	0	0	600	15-45	600	45-75	0	0
57	2	15-20	2	30-35	2	45-50	600	15-45	600	45-75	0	0
58	2	15-20	2	30-35	2	45-50	600	15-45	600	45-75	600	75-105
59	2	15-17	0	0	0	0	1000	15-45	0	0	0	0
60	4	15-17	0	0	0	0	1000	15-45	0	0	0	0
61	6	15-17	0	0	0	0	1000	15-45	0	0	0	0
62	2	15-17	2	20-22	0	0	1000	15-45	0	0	0	0
63	4	15-17	2	20-22	0	0	1000	15-45	0	0	0	0
64	6	15-17	2	20-22	0	0	1000	15-45	0	0	0	0
65	2	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0
66	4	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0
67	6	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0
68	2	15-17	0	0	0	0	1750	15-45	0	0	0	0
69	4	15-17	0	0	0	0	1750	15-45	0	0	0	0
70	6	15-17	0	0	0	0	3500	15-45	0	0	0	0
71	2	15-17	2	17-19	0	0	1750	15-45	0	0	0	0
72	4	15-17	2	17-19	0	0	1750	15-45	0	0	0	0
73	6	15-17	2	17-19	0	0	3500	15-45	0	0	0	0
74	2	15-17	2	17-19	2	19-21	1750	15-45	0	0	0	0
75	4	15-17	4	17-19	4	19-21	1750	15-45	0	0	0	0
76	6	15-17	6	17-19	6	19-21	3500	15-45	0	0	0	0
77	2	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0
78	4	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0

	Atropine						Oxime					
	Dose 1 and timing		Dose 2 and timing		Dose 3 and timing		Dose 1 and timing		Dose 2 and timing		Dose 3 and timing	
Test	**(mg)**	**(min)**	**(mg)**	**(min)**	**(mg)**	**(min)**	**(mg)**	**(min)**	**(mg)**	**(min)**	**(mg)**	**(min)**
84	4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	0	0
85	6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	0	0
86	2	15-17	0	0	0	0	1750	15-45	1750	75-105	1750	165-195
87	4	15-17	0	0	0	0	1750	15-45	1750	75-105	1750	165-195
88	6	15-17	0	0	0	0	3500	15-45	3500	75-105	3500	165-195
89	2	15-17	2	17-19	0	0	1750	15-45	1750	75-105	1750	165-195
90	4	15-17	2	17-19	0	0	1750	15-45	1750	75-105	1750	165-195
91	6	15-17	2	17-19	0	0	3500	15-45	3500	75-105	3500	165-195
92	2	15-17	2	17-19	2	19-21	1750	15-45	1750	75-105	1750	165-195
93	4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	1750	165-195
94	6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	3500	165-195
95	6	15-18	2	20-23	0	0	1800	15	0	0	0	0
96	6	15-18	2	20-23	2	25-28	1800	15	0	0	0	0
97	6	15-18	2	20-23	0	0	1800	15	1000	75-95	0	0
98	6	15-18	2	20-23	2	25-28	1800	15	1000	75-95	0	0

Appendix D – Results

Table 9 – Results from 5-minute mild exposure with IM treatment

5-minute mild exposure - IM treatment

Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	6	4	6	6	0	0	0	0	0	0	1.1971	1	0.8385	1.4905	4	no
9	2	0	0	0	0	0	0	0	0	0	0	1.2225	2	0.9443	1.4898	1	no
5	2	5	7	0	0	0	0	0	0	0	0	1.2237	3	0.9329	1.4908	17	no
6	2	6	4	6	6	1800	2	1800	32	1800	92	1.2260	4	0.8573	1.4906	6	no
6	2	6	4	6	6	1800	2	1800	32	0	0	1.2262	5	0.8621	1.4906	6	no
5	2	4	7	0	0	0	0	0	0	0	0	1.2283	6	0.9518	1.4908	17	no
8	2	0	0	0	0	0	0	0	0	0	0	1.2290	7	0.9680	1.4899	2	no
6	2	6	4	6	6	1800	2	0	0	0	0	1.2299	8	0.8920	1.4906	6	no
5	2	3	7	0	0	0	0	0	0	0	0	1.2338	9	0.9740	1.4908	17	no
7	2	0	0	0	0	0	0	0	0	0	0	1.2368	10	0.9962	1.4902	3	no
5	2	2	7	0	0	0	0	0	0	0	0	1.2402	11	1.0000	1.4908	17	no
5	2	2	12	0	0	0	0	0	0	0	0	1.2424	12	1.0000	1.4908	17	no
5	2	2	17	0	0	0	0	0	0	0	0	1.2441	13	1.0000	1.4908	17	no
5	2	2	22	0	0	0	0	0	0	0	0	1.2458	14	1.0000	1.4908	17	no
6	2	0	0	0	0	0	0	0	0	0	0	1.2461	15	1.0000	1.4905	4	no
5	2	1	7	0	0	0	0	0	0	0	0	1.2480	16	1.0000	1.4908	17	no
4	2	4	4	4	6	600	2	0	0	0	0	1.2505	17	1.0000	1.4915	27	no
4	2	4	4	4	6	600	2	600	32	600	92	1.2505	18	0.9966	1.4915	27	no
4	2	4	4	4	6	600	2	600	32	0	0	1.2505	19	0.9973	1.4915	27	no

5-minute mild exposure - IM treatment (continued)

Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	2	7	2	12	1800	2	0	0	0	0	1.2569	20	0.9865	1.4906	6	no
5	2	0	0	0	0	0	0	0	0	0	0	1.2576	21	1.0000	1.4908	17	no
6	2	2	4	0	0	1800	2	1800	32	1800	92	1.2597	22	0.9850	1.4906	6	no
6	2	2	4	0	0	1800	2	1800	32	0	0	1.2600	23	0.9905	1.4906	6	no
6	2	2	4	0	0	1800	2	0	0	0	0	1.2640	24	1.0000	1.4906	6	no
6	2	2	7	0	0	1800	2	0	0	0	0	1.2656	25	1.0000	1.4906	6	no
4	2	0	0	0	0	0	0	0	0	0	0	1.2721	26	1.0000	1.4913	26	no
4	2	2	7	2	12	600	2	0	0	0	0	1.2749	27	1.0000	1.4915	30	no
6	2	0	0	0	0	1800	2	1800	32	1800	92	1.2754	28	1.0000	1.4906	6	no
6	2	0	0	0	0	1800	2	1800	32	0	0	1.2757	29	1.0000	1.4906	6	no
2	2	2	17	2	32	0	0	0	0	0	0	1.2778	30	1.0000	1.4937	39	no
6	2	0	0	0	0	1800	2	0	0	0	0	1.2799	31	1.0000	1.4906	6	no
4	2	2	4	0	0	600	2	0	0	0	0	1.2854	32	1.0000	1.4915	30	no
4	2	2	4	0	0	600	2	600	32	600	92	1.2854	33	1.0000	1.4915	30	no
4	2	2	4	0	0	600	2	600	32	0	0	1.2855	34	1.0000	1.4915	30	no
4	2	2	7	0	0	600	2	0	0	0	0	1.2877	35	1.0000	1.4915	30	no
2	2	2	17	0	0	0	0	0	0	0	0	1.2888	36	1.0000	1.4937	39	no
2	2	2	4	2	6	600	2	0	0	0	0	1.2896	37	1.0000	1.4941	42	no
2	2	2	4	2	6	600	2	600	32	600	92	1.2897	38	1.0000	1.4941	42	no
2	2	2	4	2	6	600	2	600	32	0	0	1.2897	39	1.0000	1.4941	42	no
3	2	0	0	0	0	0	0	0	0	0	0	1.2911	40	1.0000	1.4921	38	no

5-minute mild exposure - IM treatment (continued)

Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	2	2	7	2	12	600	2	0	0	0	0	1.2969	41	1.0000	1.4955	48	no
2	2	2	12	2	22	600	2	600	12	600	22	1.3039	42	1.0000	1.4963	50	no
4	2	0	0	0	0	600	2	0	0	0	0	1.3104	43	1.0000	1.4915	30	no
4	2	0	0	0	0	600	2	600	32	600	92	1.3104	44	1.0000	1.4915	30	no
4	2	0	0	0	0	600	2	600	32	0	0	1.3105	45	1.0000	1.4915	30	no
2	2	2	4	0	0	600	2	0	0	0	0	1.3133	46	1.0000	1.4941	42	no
2	2	2	4	0	0	600	2	600	32	600	92	1.3133	47	1.0000	1.4941	42	no
2	2	2	4	0	0	600	2	600	32	0	0	1.3134	48	1.0000	1.4941	42	no
2	2	2	17	2	32	600	2	600	17	600	32	1.3155	49	1.0000	1.4969	54	no
2	2	2	17	2	32	600	2	600	17	0	0	1.3166	50	1.0000	1.4969	54	no
2	2	2	7	0	0	600	2	0	0	0	0	1.3169	51	1.0000	1.4955	48	no
2	2	2	17	2	32	600	2	0	0	0	0	1.3172	52	1.0000	1.4969	52	no
2	2	0	0	0	0	0	0	0	0	0	0	1.3195	53	1.0000	1.4937	39	no
2	2	2	12	0	0	600	2	600	12	0	0	1.3211	54	1.0000	1.4963	50	no
2	2	2	17	0	0	600	2	600	17	0	0	1.3278	55	1.0000	1.4969	54	no
2	2	2	17	0	0	600	2	0	0	0	0	1.3284	56	1.0000	1.4969	52	no
1	2	0	0	0	0	0	0	0	0	0	0	1.3552	57	1.0000	1.4996	60	no
2	2	0	0	0	0	600	2	600	32	600	92	1.3574	58	1.0000	1.4972	57	no
2	2	0	0	0	0	600	2	600	32	0	0	1.3574	59	1.0000	1.4972	57	no
2	2	0	0	0	0	600	2	0	0	0	0	1.3599	60	1.0000	1.4972	59	no

5-minute mild exposure - IM treatment (continued)

Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
0	0	0	0	0	0	0	0	0	0	0	0	1.4198	61	1.0000	1.6602	61	no
0	0	0	0	0	0	600	2	600	17	600	32	1.4614	62	1.0000	1.7675	62	no
0	0	0	0	0	0	600	2	600	17	0	0	1.4629	63	1.0000	1.7773	63	no
0	0	0	0	0	0	600	2	0	0	0	0	1.4639	64	1.0000	1.7934	64	no

Table 10 – Results from 15-minute mild exposure with IM treatment

15-minute mild exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
9	2	0	0	0	0	0	0	0	0	0	0	1.2174	1	0.9604	1.4922	1	no
6	2	6	4	6	6	1800	2	1800	32	0	0	1.2183	2	0.8576	1.4934	5	no
6	2	6	4	6	6	1800	2	1800	32	1800	92	1.2183	2	0.8576	1.4934	5	no
6	2	6	4	6	6	1800	2	0	0	0	0	1.2230	4	0.8920	1.4934	5	no
8	2	0	0	0	0	0	0	0	0	0	0	1.2244	5	0.9851	1.4925	2	no
7	2	0	0	0	0	0	0	0	0	0	0	1.2328	6	1.0000	1.4927	3	no
6	2	0	0	0	0	0	0	0	0	0	0	1.2429	7	1.0000	1.4930	4	no
4	2	4	4	4	6	600	2	600	32	0	0	1.2476	8	1.0000	1.4946	18	no
4	2	4	4	4	6	600	2	600	32	600	92	1.2476	8	1.0000	1.4946	18	no
4	2	4	4	4	6	600	2	0	0	0	0	1.2477	10	1.0000	1.4946	18	no
6	2	2	7	2	12	1800	2	0	0	0	0	1.2521	11	0.9897	1.4934	5	no
6	2	2	4	0	0	1800	2	1800	32	0	0	1.2548	12	0.9902	1.4934	5	no
6	2	2	4	0	0	1800	2	1800	32	1800	92	1.2548	12	0.9902	1.4934	5	no
5	2	0	0	0	0	0	0	0	0	0	0	1.2554	14	1.0000	1.4936	16	no
6	2	2	4	0	0	1800	2	0	0	0	0	1.2599	15	1.0000	1.4934	5	no
6	2	2	7	0	0	1800	2	0	0	0	0	1.2616	16	1.0000	1.4934	5	no
4	2	0	0	0	0	0	0	0	0	0	0	1.2711	17	1.0000	1.4943	17	no
6	2	0	0	0	0	1800	2	1800	32	0	0	1.2718	18	1.0000	1.4934	5	no
6	2	0	0	0	0	1800	2	1800	32	1800	92	1.2718	18	1.0000	1.4934	5	no

15-minute mild exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
4	2	2	7	2	12	600	2	0	0	0	0	1.2741	20	1.0000	1.4946	24	no
2	2	2	17	2	32	0	0	0	0	0	0	1.2760	21	1.0000	1.4981	30	no
6	2	0	0	0	0	1800	2	0	0	0	0	1.2771	22	1.0000	1.4934	5	no
4	2	2	4	0	0	600	2	600	32	0	0	1.2856	23	1.0000	1.4946	21	no
4	2	2	4	0	0	600	2	600	32	600	92	1.2856	23	1.0000	1.4946	21	no
4	2	2	4	0	0	600	2	0	0	0	0	1.2857	25	1.0000	1.4946	21	no
4	2	2	7	0	0	600	2	0	0	0	0	1.2881	26	1.0000	1.4946	24	no
2	2	2	17	0	0	0	0	0	0	0	0	1.2885	27	1.0000	1.4981	30	no
2	2	2	4	2	6	600	2	600	32	0	0	1.2900	28	1.0000	1.4982	33	no
2	2	2	4	2	6	600	2	600	32	600	92	1.2900	28	1.0000	1.4982	33	no
2	2	2	4	2	6	600	2	0	0	0	0	1.2902	30	1.0000	1.4982	33	no
3	2	0	0	0	0	0	0	0	0	0	0	1.2918	31	1.0000	1.4955	29	no
2	2	2	7	2	12	600	2	0	0	0	0	1.2977	32	1.0000	1.5018	39	no
2	2	2	12	2	22	600	2	600	12	600	22	1.3035	33	1.0000	1.5066	41	no
4	2	0	0	0	0	600	2	600	32	0	0	1.3128	34	1.0000	1.4946	24	no
4	2	0	0	0	0	600	2	600	32	600	92	1.3128	34	1.0000	1.4946	24	no
4	2	0	0	0	0	600	2	0	0	0	0	1.3130	36	1.0000	1.4946	24	no
2	2	2	4	0	0	600	2	600	32	0	0	1.3158	37	1.0000	1.4982	33	no
2	2	2	4	0	0	600	2	600	32	600	92	1.3158	37	1.0000	1.4982	33	no
2	2	2	4	0	0	600	2	0	0	0	0	1.3160	39	1.0000	1.4982	33	no
2	2	2	17	2	32	600	2	600	17	600	32	1.3161	40	1.0000	1.5109	46	no

15-minute mild exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	2	2	17	2	32	600	2	600	17	0	0	1.3176	41	1.0000	1.5109	46	no
2	2	2	17	2	32	600	2	0	0	0	0	1.3189	42	1.0000	1.5109	44	no
2	2	2	7	0	0	600	2	0	0	0	0	1.3197	43	1.0000	1.5018	39	no
2	2	0	0	0	0	0	0	0	0	0	0	1.3224	44	1.0000	1.4981	30	no
2	2	2	12	0	0	600	2	600	12	0	0	1.3231	45	1.0000	1.5066	41	no
2	2	2	17	0	0	600	2	600	17	0	0	1.3303	46	1.0000	1.5109	46	no
2	2	2	17	0	0	600	2	0	0	0	0	1.3316	47	1.0000	1.5109	44	no
1	2	0	0	0	0	0	0	0	0	0	0	1.3614	48	1.0000	1.5083	43	no
2	2	0	0	0	0	600	2	600	32	0	0	1.3637	49	1.0000	1.5181	50	no
2	2	0	0	0	0	600	2	600	32	600	92	1.3637	49	1.0000	1.5181	50	no
2	2	0	0	0	0	600	2	0	0	0	0	1.3664	51	1.0000	1.5181	49	no
0	0	0	0	0	0	0	0	0	0	0	0	1.4308	52	1.0000	1.7045	52	no
0	0	0	0	0	0	600	2	600	17	600	32	1.4751	53	1.0000	1.8039	53	no
0	0	0	0	0	0	600	2	600	17	0	0	1.4772	54	1.0000	1.8154	54	no
0	0	0	0	0	0	600	2	0	0	0	0	1.4792	55	1.0000	1.8359	55	no

Table 11 – Results from 30-minute mild exposure with IM treatment

30-minute mild exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	6	4	6	6	0	0	0	0	0	0	1.1927	1	0.8864	1.4948	1	
6	2	6	4	6	6	1800	2	1800	32	0	0	1.2205	2	0.8968	1.4953	2	no
6	2	6	4	6	6	1800	2	1800	32	1800	92	1.2205	2	0.8968	1.4953	2	no
6	2	6	4	6	6	1800	2	0	0	0	0	1.2247	4	0.9304	1.4953	2	no
4	2	4	4	4	6	600	2	600	32	0	0	1.2481	5	1.0000	1.4967	13	no
4	2	4	4	4	6	600	2	600	32	600	92	1.2481	5	1.0000	1.4967	13	no
4	2	4	4	4	6	600	2	0	0	0	0	1.2482	7	1.0000	1.4967	13	no
6	2	2	7	2	12	1800	2	0	0	0	0	1.2520	8	1.0000	1.4953	8	no
6	2	2	4	0	0	1800	2	1800	32	0	0	1.2546	9	1.0000	1.4953	5	no
6	2	2	4	0	0	1800	2	1800	32	1800	92	1.2546	9	1.0000	1.4953	5	no
6	2	2	4	0	0	1800	2	0	0	0	0	1.2591	11	1.0000	1.4953	5	no
6	2	2	7	0	0	1800	2	0	0	0	0	1.2607	12	1.0000	1.4953	8	no
6	2	0	0	0	0	1800	2	1800	32	0	0	1.2704	13	1.0000	1.4953	8	no
6	2	0	0	0	0	1800	2	1800	32	1800	92	1.2704	13	1.0000	1.4953	8	no
4	2	2	7	2	12	600	2	0	0	0	0	1.2731	15	1.0000	1.4968	19	no
2	2	2	17	2	32	0	0	0	0	0	0	1.2748	16	1.0000	1.5011	24	no
6	2	0	0	0	0	1800	2	0	0	0	0	1.2751	17	1.0000	1.4953	8	no
4	2	2	4	0	0	600	2	600	32	0	0	1.2835	18	1.0000	1.4967	16	no
4	2	2	4	0	0	600	2	600	32	600	92	1.2835	18	1.0000	1.4967	16	no

30-minute mild exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
4	2	2	4	0	0	600	2	0	0	0	0	1.2836	20	1.0000	1.4967	16	no
2	2	2	17	0	0	0	0	0	0	0	0	1.2858	21	1.0000	1.5011	24	no
4	2	2	7	0	0	600	2	0	0	0	0	1.2859	22	1.0000	1.4968	19	no
2	2	2	4	2	6	600	2	600	32	0	0	1.2879	23	1.0000	1.5012	27	no
2	2	2	4	2	6	600	2	600	32	600	92	1.2879	23	1.0000	1.5012	27	no
2	2	2	4	2	6	600	2	0	0	0	0	1.2880	25	1.0000	1.5012	27	no
2	2	2	7	2	12	600	2	0	0	0	0	1.2954	26	1.0000	1.5062	33	no
2	2	2	12	2	22	600	2	600	12	600	22	1.3012	27	1.0000	1.5138	35	no
4	2	0	0	0	0	600	2	600	32	0	0	1.3088	28	1.0000	1.4968	19	no
4	2	0	0	0	0	600	2	600	32	600	92	1.3088	28	1.0000	1.4968	19	no
4	2	0	0	0	0	600	2	0	0	0	0	1.3090	30	1.0000	1.4968	19	no
2	2	2	4	0	0	600	2	600	32	0	0	1.3118	31	1.0000	1.5012	30	no
2	2	2	4	0	0	600	2	600	32	600	92	1.3118	31	1.0000	1.5012	30	no
2	2	2	4	0	0	600	2	0	0	0	0	1.3119	33	1.0000	1.5012	30	no
2	2	2	17	2	32	600	2	600	17	600	32	1.3135	34	1.0000	1.5202	39	no
2	2	2	17	2	32	600	2	600	17	0	0	1.3149	35	1.0000	1.5202	39	no
2	2	2	7	0	0	600	2	0	0	0	0	1.3156	36	1.0000	1.5062	33	no
2	2	2	17	2	32	600	2	0	0	0	0	1.3161	37	1.0000	1.5201	37	no
2	2	0	0	0	0	0	0	0	0	0	0	1.3168	38	1.0000	1.5011	24	no
2	2	2	12	0	0	600	2	600	12	0	0	1.3189	39	1.0000	1.5138	35	no
2	2	2	17	0	0	600	2	600	17	0	0	1.3261	40	1.0000	1.5202	39	no

30-minute mild exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	2	2	17	0	0	600	2	0	0	0	0	1.3274	41	1.0000	1.5201	37	no
2	2	0	0	0	0	600	2	600	32	0	0	1.3564	42	1.0000	1.5337	43	no
2	2	0	0	0	0	600	2	600	32	600	92	1.3564	42	1.0000	1.5337	43	no
2	2	0	0	0	0	600	2	0	0	0	0	1.3592	44	1.0000	1.5335	42	no
0	0	0	0	0	0	0	0	0	0	0	0	1.4187	45	1.0000	1.7274	45	no
0	0	0	0	0	0	600	2	600	17	600	32	1.4609	46	1.0000	1.8264	46	no
0	0	0	0	0	0	600	2	600	17	0	0	1.4627	47	1.0000	1.8389	47	no
0	0	0	0	0	0	600	2	0	0	0	0	1.4646	48	1.0000	1.8615	48	no

Table 12 – Results from 5-minute severe exposure with IM treatment

5-minute severe exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	6	4	6	6	0	0	0	0	0	0	1.1793	1	0.8435	1.5057	4	no
6	2	6	4	6	6	1800	2	1800	32	1800	92	1.1855	2	0.7338	1.5079	7	no
6	2	6	4	6	6	1800	2	1800	32	0	0	1.1857	3	0.7366	1.5079	7	no
6	2	6	4	6	6	1800	2	0	0	0	0	1.1994	4	0.7938	1.5079	7	no
9	2	0	0	0	0	0	0	0	0	0	0	1.2287	5	0.9900	1.5033	1	no
8	2	0	0	0	0	0	0	0	0	0	0	1.2406	6	1.0000	1.5041	2	no
6	2	2	4	0	0	1800	2	1800	32	1800	92	1.2459	7	0.8920	1.5102	13	no
6	2	2	4	0	0	1800	2	1800	32	0	0	1.2461	8	0.8953	1.5102	13	no
6	2	2	7	2	12	1800	2	0	0	0	0	1.2462	9	0.9106	1.5133	20	no
7	2	0	0	0	0	0	0	0	0	0	0	1.2547	10	1.0000	1.5049	3	no
4	2	4	4	4	6	600	2	600	32	0	0	1.2564	11	0.9608	1.5101	10	no
4	2	4	4	4	6	600	2	600	32	600	92	1.2564	12	0.9607	1.5101	10	no
4	2	4	4	4	6	600	2	0	0	0	0	1.2592	13	0.9803	1.5101	10	no
6	2	2	4	0	0	1800	2	0	0	0	0	1.2612	14	0.9604	1.5102	13	no
6	2	2	7	0	0	1800	2	0	0	0	0	1.2631	15	0.9617	1.5133	20	no
6	2	0	0	0	0	0	0	0	0	0	0	1.2717	16	1.0000	1.5061	5	no
6	2	0	0	0	0	1800	2	1800	32	1800	92	1.2737	17	0.9633	1.5156	25	no
6	2	0	0	0	0	1800	2	1800	32	0	0	1.2739	18	0.9669	1.5156	25	no
6	2	0	0	0	0	1800	2	0	0	0	0	1.2897	19	1.0000	1.5156	25	no

5-minute severe exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
5	2	0	0	0	0	0	0	0	0	0	0	1.2926	20	1.0000	1.5077	6	no
4	2	2	7	2	12	600	2	0	0	0	0	1.3018	21	1.0000	1.5156	23	no
2	2	2	17	2	32	0	0	0	0	0	0	1.3131	22	1.0000	1.5269	34	no
4	2	0	0	0	0	0	0	0	0	0	0	1.3192	23	1.0000	1.5102	16	no
4	2	2	4	0	0	600	2	600	32	0	0	1.3210	24	1.0000	1.5115	17	no
4	2	2	4	0	0	600	2	600	32	600	92	1.3210	25	1.0000	1.5115	17	no
4	2	2	4	0	0	600	2	0	0	0	0	1.3242	26	1.0000	1.5115	17	no
2	2	2	4	2	6	600	2	600	32	0	0	1.3266	27	1.0000	1.5211	28	no
2	2	2	4	2	6	600	2	600	32	600	92	1.3266	28	1.0000	1.5211	28	no
4	2	2	7	0	0	600	2	0	0	0	0	1.3271	29	1.0000	1.5156	23	no
2	2	2	4	2	6	600	2	0	0	0	0	1.3297	30	1.0000	1.5211	28	no
2	2	2	12	2	22	600	2	600	12	600	22	1.3321	31	1.0000	1.5590	42	no
2	2	2	7	2	12	600	2	0	0	0	0	1.3392	32	1.0000	1.5373	40	no
2	2	2	17	0	0	0	0	0	0	0	0	1.3404	33	1.0000	1.5269	34	no
2	2	2	17	2	32	600	2	600	17	600	32	1.3509	34	1.0000	1.5709	46	no
3	2	0	0	0	0	0	0	0	0	0	0	1.3539	35	1.0000	1.5149	22	no
2	2	2	17	2	32	600	2	600	17	0	0	1.3567	36	1.0000	1.5709	46	no
2	2	2	17	2	32	600	2	0	0	0	0	1.3654	37	1.0000	1.5698	44	no
4	2	0	0	0	0	600	2	600	32	0	0	1.3668	38	1.0000	1.5242	31	no
4	2	0	0	0	0	600	2	600	32	600	92	1.3668	39	1.0000	1.5242	31	no
4	2	0	0	0	0	600	2	0	0	0	0	1.3702	40	1.0000	1.5242	31	no

5-minute severe exposure - IM treatment																	
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	2	2	4	0	0	600	2	600	32	0	0	1.3705	41	1.0000	1.5323	37	no
2	2	2	4	0	0	600	2	600	32	600	92	1.3705	42	1.0000	1.5323	37	no
2	2	2	12	0	0	600	2	600	12	0	0	1.3736	43	1.0000	1.5596	43	no
2	2	2	4	0	0	600	2	0	0	0	0	1.3740	44	1.0000	1.5323	37	no
2	2	2	7	0	0	600	2	0	0	0	0	1.3786	45	1.0000	1.5425	41	no
2	2	2	17	0	0	600	2	600	17	0	0	1.3838	46	1.0000	1.5709	46	no
2	2	2	17	0	0	600	2	0	0	0	0	1.3929	47	1.0000	1.5698	44	no
2	2	0	0	0	0	0	0	0	0	0	0	1.4039	48	1.0000	1.5269	34	no
2	2	0	0	0	0	600	2	600	32	0	0	1.4506	49	1.0000	1.6123	50	no
2	2	0	0	0	0	600	2	600	32	600	92	1.4506	50	1.0000	1.6123	50	no
2	2	0	0	0	0	600	2	0	0	0	0	1.4572	51	1.0000	1.6113	49	no
1	2	0	0	0	0	0	0	0	0	0	0	1.4704	52	1.0000	1.6231	52	no
0	0	0	0	0	0	0	0	0	0	0	0	1.5841	53	1.0000	1.9020	53	yes
0	0	0	0	0	0	600	2	600	17	600	32	1.6214	54	1.0000	1.9221	54	yes
0	0	0	0	0	0	600	2	600	17	0	0	1.6296	55	1.0000	1.9390	55	yes
0	0	0	0	0	0	600	2	0	0	0	0	1.6419	56	1.0000	1.9749	56	yes

Table 13 – Results from 15-minute severe exposure with IM treatment

15-minute severe exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	6	4	6	6	0	0	0	0	0	0	1.1855	1	0.8682	1.5063	1	no
6	2	6	4	6	6	1800	2	1800	32	1800	92	1.1933	2	0.7639	1.5087	2	no
6	2	6	4	6	6	1800	2	1800	32	0	0	1.1934	3	0.7660	1.5087	2	no
6	2	6	4	6	6	1800	2	0	0	0	0	1.2058	4	0.8223	1.5087	2	no
6	2	2	4	0	0	1800	2	1800	32	1800	92	1.2498	5	0.9192	1.5116	8	no
6	2	2	7	2	12	1800	2	0	0	0	0	1.2498	6	0.9370	1.5149	14	no
6	2	2	4	0	0	1800	2	1800	32	0	0	1.2499	7	0.9217	1.5116	8	no
4	2	4	4	4	6	600	2	600	32	0	0	1.2594	8	0.9888	1.5108	5	no
4	2	4	4	4	6	600	2	600	32	600	92	1.2594	9	0.9888	1.5108	5	no
4	2	4	4	4	6	600	2	0	0	0	0	1.2619	10	1.0000	1.5108	5	no
6	2	2	4	0	0	1800	2	0	0	0	0	1.2636	11	0.9855	1.5116	8	no
6	2	2	7	0	0	1800	2	0	0	0	0	1.2655	12	0.9868	1.5149	14	no
6	2	0	0	0	0	1800	2	1800	32	1800	92	1.2758	13	0.9894	1.5177	18	no
6	2	0	0	0	0	1800	2	1800	32	0	0	1.2760	14	0.9921	1.5177	18	no
6	2	0	0	0	0	1800	2	0	0	0	0	1.2903	15	1.0000	1.5177	18	no
4	2	2	7	2	12	600	2	0	0	0	0	1.3019	16	1.0000	1.5172	16	no
2	2	2	17	2	32	0	0	0	0	0	0	1.3125	17	1.0000	1.5292	27	no
4	2	2	4	0	0	600	2	600	32	0	0	1.3198	18	1.0000	1.5127	11	no
4	2	2	4	0	0	600	2	600	32	600	92	1.3198	19	1.0000	1.5127	11	no

15-minute severe exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
4	2	2	4	0	0	600	2	0	0	0	0	1.3226	20	1.0000	1.5127	11	no
2	2	2	4	2	6	600	2	600	32	0	0	1.3253	21	1.0000	1.5227	21	no
2	2	2	4	2	6	600	2	600	32	600	92	1.3253	22	1.0000	1.5227	21	no
4	2	2	7	0	0	600	2	0	0	0	0	1.3254	23	1.0000	1.5172	16	no
2	2	2	4	2	6	600	2	0	0	0	0	1.3280	24	1.0000	1.5227	21	no
2	2	2	12	2	22	600	2	600	12	600	22	1.3316	25	1.0000	1.5625	35	no
2	2	2	17	0	0	0	0	0	0	0	0	1.3372	26	1.0000	1.5292	27	no
2	2	2	7	2	12	600	2	0	0	0	0	1.3372	27	1.0000	1.5397	33	no
2	2	2	17	2	32	600	2	600	17	600	32	1.3500	28	1.0000	1.5748	39	no
2	2	2	17	2	32	600	2	600	17	0	0	1.3552	29	1.0000	1.5748	39	no
4	2	0	0	0	0	600	2	600	32	0	0	1.3627	30	1.0000	1.5277	24	no
4	2	0	0	0	0	600	2	600	32	600	92	1.3627	31	1.0000	1.5277	24	no
2	2	2	17	2	32	600	2	0	0	0	0	1.3631	32	1.0000	1.5737	37	no
4	2	0	0	0	0	600	2	0	0	0	0	1.3656	33	1.0000	1.5277	24	no
2	2	2	4	0	0	600	2	600	32	0	0	1.3663	34	1.0000	1.5358	30	no
2	2	2	4	0	0	600	2	600	32	600	92	1.3663	35	1.0000	1.5358	30	no
2	2	2	4	0	0	600	2	0	0	0	0	1.3693	36	1.0000	1.5358	30	no
2	2	2	12	0	0	600	2	600	12	0	0	1.3697	37	1.0000	1.5633	36	no
2	2	2	7	0	0	600	2	0	0	0	0	1.3738	38	1.0000	1.5460	34	no
2	2	2	17	0	0	600	2	600	17	0	0	1.3798	39	1.0000	1.5748	39	no
2	2	2	17	0	0	600	2	0	0	0	0	1.3880	40	1.0000	1.5737	37	no

15-minute severe exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	2	0	0	0	0	0	0	0	0	0	0	1.3959	41	1.0000	1.5292	29	no
2	2	0	0	0	0	600	2	600	32	0	0	1.4414	42	1.0000	1.6182	43	no
2	2	0	0	0	0	600	2	600	32	600	92	1.4414	43	1.0000	1.6182	43	no
2	2	0	0	0	0	600	2	0	0	0	0	1.4474	44	1.0000	1.6173	42	no
0	0	0	0	0	0	0	0	0	0	0	0	1.5653	45	1.0000	1.9094	45	yes
0	0	0	0	0	0	600	2	600	17	600	32	1.6029	46	1.0000	1.9290	46	yes
0	0	0	0	0	0	600	2	600	17	0	0	1.6101	47	1.0000	1.9463	47	yes
0	0	0	0	0	0	600	2	0	0	0	0	1.6212	48	1.0000	1.9833	48	yes

Table 14 – Results from 30-minute severe exposure with IM treatment

30-minute severe exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	6	4	6	6	0	0	0	0	0	0	1.1928	1	0.9028	1.5062	1	no
6	2	6	4	6	6	1800	2	1800	32	1800	92	1.2054	2	0.8185	1.5086	2	no
6	2	6	4	6	6	1800	2	1800	32	0	0	1.2055	3	0.8194	1.5086	2	no
6	2	6	4	6	6	1800	2	0	0	0	0	1.2153	4	0.8721	1.5086	2	no
6	2	2	7	2	12	1800	2	0	0	0	0	1.2542	5	0.9823	1.5150	14	no
6	2	2	4	0	0	1800	2	1800	32	1800	92	1.2549	6	0.9676	1.5116	8	no
6	2	2	4	0	0	1800	2	1800	32	0	0	1.2549	7	0.9687	1.5116	8	no
4	2	4	4	4	6	600	2	600	32	0	0	1.2615	8	1.0000	1.5107	5	no
4	2	4	4	4	6	600	2	600	32	600	92	1.2615	9	1.0000	1.5107	5	no
4	2	4	4	4	6	600	2	0	0	0	0	1.2632	10	1.0000	1.5107	5	no
6	2	2	4	0	0	1800	2	0	0	0	0	1.2658	11	1.0000	1.5116	8	no
6	2	2	7	0	0	1800	2	0	0	0	0	1.2676	12	1.0000	1.5150	14	no
6	2	0	0	0	0	1800	2	1800	32	1800	92	1.2778	13	1.0000	1.5179	18	no
6	2	0	0	0	0	1800	2	1800	32	0	0	1.2778	14	1.0000	1.5179	18	no
6	2	0	0	0	0	1800	2	0	0	0	0	1.2891	15	1.0000	1.5179	18	no
4	2	2	7	2	12	600	2	0	0	0	0	1.2986	16	1.0000	1.5172	16	no
2	2	2	17	2	32	0	0	0	0	0	0	1.3066	17	1.0000	1.5288	27	no
4	2	2	4	0	0	600	2	600	32	0	0	1.3141	18	1.0000	1.5126	11	no
4	2	2	4	0	0	600	2	600	32	600	92	1.3141	19	1.0000	1.5126	11	no

30-minute severe exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
4	2	2	4	0	0	600	2	0	0	0	0	1.3159	20	1.0000	1.5126	11	no
4	2	2	7	0	0	600	2	0	0	0	0	1.3187	21	1.0000	1.5172	16	no
2	2	2	4	2	6	600	2	600	32	0	0	1.3193	22	1.0000	1.5227	21	no
2	2	2	4	2	6	600	2	600	32	600	92	1.3193	23	1.0000	1.5227	21	no
2	2	2	4	2	6	600	2	0	0	0	0	1.3211	24	1.0000	1.5227	21	no
2	2	2	17	0	0	0	0	0	0	0	0	1.3268	25	1.0000	1.5288	27	no
2	2	2	12	2	22	600	2	600	12	600	22	1.3276	26	1.0000	1.5629	35	no
2	2	2	7	2	12	600	2	0	0	0	0	1.3300	27	1.0000	1.5399	33	no
2	2	2	17	2	32	600	2	600	17	600	32	1.3446	28	1.0000	1.5753	39	no
2	2	2	17	2	32	600	2	600	17	0	0	1.3486	29	1.0000	1.5753	39	no
4	2	0	0	0	0	600	2	600	32	0	0	1.3515	30	1.0000	1.5281	24	no
4	2	0	0	0	0	600	2	600	32	600	92	1.3515	30	1.0000	1.5281	24	no
4	2	0	0	0	0	600	2	0	0	0	0	1.3535	32	1.0000	1.5281	24	no
2	2	2	17	2	32	600	2	0	0	0	0	1.3547	33	1.0000	1.5741	37	no
2	2	2	4	0	0	600	2	600	32	0	0	1.3550	34	1.0000	1.5361	30	no
2	2	2	4	0	0	600	2	600	32	600	92	1.3550	35	1.0000	1.5361	30	no
2	2	2	4	0	0	600	2	0	0	0	0	1.3570	36	1.0000	1.5361	30	no
2	2	2	12	0	0	600	2	600	12	0	0	1.3592	37	1.0000	1.5638	36	no
2	2	2	7	0	0	600	2	0	0	0	0	1.3614	38	1.0000	1.5465	34	no
2	2	2	17	0	0	600	2	600	17	0	0	1.3687	39	1.0000	1.5753	39	no
2	2	2	17	0	0	600	2	0	0	0	0	1.3751	40	1.0000	1.5741	37	no

30-minute severe exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	2	0	0	0	0	0	0	0	0	0	0	1.3766	41	1.0000	1.5288	29	no
2	2	0	0	0	0	600	2	600	32	0	0	1.4207	42	1.0000	1.6192	43	no
2	2	0	0	0	0	600	2	600	32	600	92	1.4207	42	1.0000	1.6192	43	no
2	2	0	0	0	0	600	2	0	0	0	0	1.4257	44	1.0000	1.6182	42	no
0	0	0	0	0	0	0	0	0	0	0	0	1.5254	45	1.0000	1.9011	45	yes
0	0	0	0	0	0	600	2	600	17	600	32	1.5648	46	1.0000	1.9303	46	yes
0	0	0	0	0	0	600	2	600	17	0	0	1.5702	47	1.0000	1.9477	47	yes
0	0	0	0	0	0	600	2	0	0	0	0	1.5786	48	1.0000	1.9849	48	yes

Table 15 – Results from 5-minute lethal exposure with IM treatment

5-minute lethal exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	6	4	6	6	0	0	0	0	0	0	1.2488	1	0.9663	1.5310	2	no
6	2	2	7	2	12	1800	2	0	0	0	0	1.2677	2	0.9057	1.5600	7	no
6	2	2	7	0	0	1800	2	0	0	0	0	1.2902	3	0.9628	1.5612	8	no
9	2	0	0	0	0	0	0	0	0	0	0	1.3172	4	1.0000	1.5284	1	no
6	2	0	0	0	0	1800	2	0	0	0	0	1.3249	5	1.0000	1.5695	10	no
8	2	0	0	0	0	0	0	0	0	0	0	1.3333	6	1.0000	1.5312	3	no
7	2	0	0	0	0	0	0	0	0	0	0	1.3524	7	1.0000	1.5348	4	no
4	2	2	7	2	12	600	2	0	0	0	0	1.3647	8	1.0000	1.5748	11	no
6	2	6	4	6	6	1800	2	1800	32	1800	92	1.3655	9	0.8207	1.8458	28	no
6	2	6	4	6	6	1800	2	1800	32	0	0	1.3663	10	0.8287	1.8458	28	no
6	2	0	0	0	0	0	0	0	0	0	0	1.3755	11	1.0000	1.5401	5	no
2	2	2	12	2	22	600	2	600	12	600	22	1.3860	12	1.0000	1.6399	19	no
6	2	6	4	6	6	1800	2	0	0	0	0	1.3956	13	0.9205	1.8459	30	no
4	2	2	7	0	0	600	2	0	0	0	0	1.3989	14	1.0000	1.5829	12	no
5	2	0	0	0	0	0	0	0	0	0	0	1.4039	15	1.0000	1.5484	6	no
2	2	2	17	2	32	600	2	600	17	600	32	1.4112	16	1.0000	1.6625	22	no
6	2	2	4	0	0	1800	2	1800	32	1800	92	1.4124	17	0.9621	1.8460	31	no
2	2	2	7	2	12	600	2	0	0	0	0	1.4127	18	1.0000	1.6099	16	no
6	2	2	4	0	0	1800	2	1800	32	0	0	1.4133	19	0.9712	1.8460	31	no

5-minute lethal exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	2	2	17	2	32	600	2	600	17	0	0	1.4226	20	1.0000	1.6625	23	no
2	2	2	17	2	32	0	0	0	0	0	0	1.4249	21	1.0000	1.6094	14	no
6	2	0	0	0	0	1800	2	1800	32	1800	92	1.4341	22	1.0000	1.8461	34	no
6	2	0	0	0	0	1800	2	1800	32	0	0	1.4351	23	1.0000	1.8461	34	no
4	2	0	0	0	0	0	0	0	0	0	0	1.4398	24	1.0000	1.5632	9	no
2	2	2	17	2	32	600	2	0	0	0	0	1.4424	25	1.0000	1.6622	21	no
6	2	2	4	0	0	1800	2	0	0	0	0	1.4443	26	1.0000	1.8461	33	no
2	2	2	12	0	0	600	2	600	12	0	0	1.4472	27	1.0000	1.6476	20	no
4	2	0	0	0	0	600	2	0	0	0	0	1.4560	28	1.0000	1.6167	17	no
2	2	2	17	0	0	600	2	600	17	0	0	1.4610	29	1.0000	1.6632	24	no
2	2	2	17	0	0	0	0	0	0	0	0	1.4651	30	1.0000	1.6094	14	no
2	2	2	7	0	0	600	2	0	0	0	0	1.4656	31	1.0000	1.6346	18	no
2	2	2	17	0	0	600	2	0	0	0	0	1.4816	32	1.0000	1.6635	25	no
3	2	0	0	0	0	0	0	0	0	0	0	1.4867	33	1.0000	1.5971	13	no
4	2	4	4	4	6	600	2	600	32	600	92	1.4875	34	1.0000	1.8743	37	no
4	2	4	4	4	6	600	2	600	32	0	0	1.4875	35	1.8743	1.8743	37	no
4	2	4	4	4	6	600	2	0	0	0	0	1.4966	36	1.0000	1.8742	36	no
4	2	2	4	0	0	600	2	600	32	600	92	1.5387	37	1.0000	1.8761	40	no
4	2	2	4	0	0	600	2	600	32	0	0	1.5387	38	1.0000	1.8761	40	no
2	2	2	4	2	6	600	2	600	32	600	92	1.5437	39	1.0000	1.8850	46	no
2	2	2	4	2	6	600	2	600	32	0	0	1.5438	40	1.0000	1.8850	46	no

5-minute lethal exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
4	2	2	4	0	0	600	2	0	0	0	0	1.5484	41	1.0000	1.8761	39	no
2	2	2	4	2	6	600	2	0	0	0	0	1.5535	42	1.0000	1.8849	45	no
2	2	0	0	0	0	0	0	0	0	0	0	1.5536	43	1.0000	1.6889	26	no
2	2	0	0	0	0	600	2	0	0	0	0	1.5684	44	1.0000	1.7376	27	no
4	2	0	0	0	0	600	2	600	32	600	92	1.5751	45	1.0000	1.8804	42	no
4	2	0	0	0	0	600	2	600	32	0	0	1.5752	46	1.0000	1.8804	42	no
2	2	2	4	0	0	600	2	600	32	600	92	1.5785	47	1.0000	1.8876	49	no
2	2	2	4	0	0	600	2	600	32	0	0	1.5786	48	1.0000	1.8876	49	no
2	2	2	4	0	0	600	2	0	0	0	0	1.5887	49	1.0000	1.8873	48	no
2	2	0	0	0	0	600	2	600	32	600	92	1.6425	50	1.0000	1.9097	51	yes
2	2	0	0	0	0	600	2	600	32	0	0	1.6426	51	1.0000	1.9097	51	yes
1	2	0	0	0	0	0	0	0	0	0	0	1.6434	52	1.0000	1.8837	44	no
0	0	0	0	0	0	600	2	600	17	600	32	1.7632	53	1.0000	2.0602	53	yes
0	0	0	0	0	0	600	2	600	17	0	0	1.7792	54	1.0000	2.0837	54	yes
0	0	0	0	0	0	0	0	0	0	0	0	1.7948	55	1.0000	2.2021	56	yes
0	0	0	0	0	0	600	2	0	0	0	0	1.8067	56	1.0000	2.1398	55	yes

Table 16 – Results from 15-minute lethal exposure with IM treatment

15-minute lethal exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	6	4	6	6	1800	2	1800	32	1800	92	1.1906	1	0.7168	1.5414	2	no
6	2	6	4	6	6	1800	2	1800	32	0	0	1.1912	2	0.7229	1.5414	2	no
6	2	0	0	0	0	5000	2	0	0	0	0	1.2081	3	0.8167	1.5610	15	no
6	2	6	4	6	6	1800	2	0	0	0	0	1.2132	4	0.7974	1.5414	2	no
6	2	0	0	0	0	4500	2	0	0	0	0	1.2219	5	0.8411	1.5622	17	no
6	2	0	0	0	0	4000	2	0	0	0	0	1.2371	6	0.8695	1.5635	20	no
6	2	6	4	6	6	0	0	0	0	0	0	1.2529	7	0.9874	1.5319	1	no
6	2	0	0	0	0	3500	2	0	0	0	0	1.2539	8	0.9025	1.5650	21	no
6	2	2	4	0	0	1800	2	1800	32	1800	92	1.2647	9	0.8872	1.5587	12	no
6	2	2	4	0	0	1800	2	1800	32	0	0	1.2654	10	0.8945	1.5587	12	no
6	2	2	7	2	12	1800	2	0	0	0	0	1.2707	11	0.9248	1.5618	16	no
6	2	0	0	0	0	3000	2	0	0	0	0	1.2725	12	0.9410	1.5667	22	no
6	2	2	4	0	0	1800	2	0	0	0	0	1.2899	13	0.9799	1.5587	12	no
6	2	2	7	0	0	1800	2	0	0	0	0	1.2920	14	0.9810	1.5631	18	no
6	2	0	0	0	0	2500	2	0	0	0	0	1.2929	15	0.9859	1.5686	23	no
6	2	0	0	0	0	1800	2	1800	32	1800	92	1.2987	16	0.9634	1.5716	26	no
6	2	0	0	0	0	1800	2	1800	32	0	0	1.2994	17	0.9712	1.5716	26	no
4	2	4	4	4	6	600	2	600	32	600	92	1.3043	18	1.0000	1.5488	7	no
4	2	4	4	4	6	600	2	600	32	0	0	1.3043	19	1.0000	1.5488	7	no

15-minute lethal exposure - IM treatment																	
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
4	2	4	4	4	6	600	2	0	0	0	0	1.3112	20	1.0000	1.5488	7	no
6	2	2	17	2	32	2000	2	0	0	0	0	1.3155	21	1.0000	1.5707	24	no
6	2	0	0	0	0	2000	2	0	0	0	0	1.3155	21	1.0000	1.5707	24	no
6	2	0	0	0	0	1800	2	0	0	0	0	1.3251	23	1.0000	1.5716	26	no
6	2	0	0	0	0	1500	2	0	0	0	0	1.3402	24	1.0000	1.5729	30	no
4	2	2	7	2	12	600	2	0	0	0	0	1.3640	25	1.0000	1.5777	33	no
6	2	0	0	0	0	1000	2	0	0	0	0	1.3672	26	1.0000	1.5746	32	no
6	2	0	0	0	0	0	0	0	0	0	0	1.3735	27	1.0000	1.5420	5	no
6	2	0	0	0	0	750	2	0	0	0	0	1.3815	28	1.0000	1.5745	31	no
4	2	2	4	0	0	600	2	600	32	600	92	1.3854	29	1.0000	1.5795	34	no
4	2	2	4	0	0	600	2	600	32	0	0	1.3854	30	1.0000	1.5795	34	no
2	2	2	12	2	22	600	2	600	12	600	22	1.3855	31	1.0000	1.6432	51	no
6	2	0	0	0	0	50	2	0	0	0	0	1.3916	32	1.0000	1.5454	6	no
2	2	2	4	2	6	600	2	600	32	600	92	1.3917	33	1.0000	1.5917	38	no
2	2	2	4	2	6	600	2	600	32	0	0	1.3917	34	1.0000	1.5917	38	no
4	2	2	4	0	0	600	2	0	0	0	0	1.3932	35	1.0000	1.5795	34	no
6	2	0	0	0	0	500	2	0	0	0	0	1.3956	36	1.0000	1.5723	29	no
4	2	2	7	0	0	600	2	0	0	0	0	1.3965	37	1.0000	1.5862	37	no
2	2	2	4	2	6	600	2	0	0	0	0	1.3995	38	1.0000	1.5917	38	no
6	2	0	0	0	0	100	2	0	0	0	0	1.4003	39	1.0000	1.5500	10	no
6	2	0	0	0	0	150	2	0	0	0	0	1.4043	40	1.0000	1.5551	11	no

15-minute lethal exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	0	0	0	0	250	2	0	0	0	0	1.4056	41	1.0000	1.5633	19	no
2	2	2	7	2	12	600	2	0	0	0	0	1.4101	42	1.0000	1.6133	43	no
2	2	2	17	2	32	600	2	600	17	600	32	1.4102	43	1.0000	1.6662	54	no
2	2	2	17	2	32	600	2	600	17	0	0	1.4208	44	1.0000	1.6662	55	no
2	2	2	17	2	32	0	0	0	0	0	0	1.4224	45	1.0000	1.6131	41	no
2	2	2	17	2	32	600	2	0	0	0	0	1.4396	46	1.0000	1.6660	53	no
4	2	0	0	0	0	600	2	600	32	600	92	1.4425	47	1.0000	1.6209	45	no
4	2	0	0	0	0	600	2	600	32	0	0	1.4426	48	1.0000	1.6209	45	no
2	2	2	12	0	0	600	2	600	12	0	0	1.4432	49	1.0000	1.6513	52	no
2	2	2	4	0	0	600	2	600	32	600	92	1.4468	50	1.0000	1.6287	48	no
2	2	2	4	0	0	600	2	600	32	0	0	1.4468	51	1.0000	1.6287	48	no
4	2	0	0	0	0	600	2	0	0	0	0	1.4509	52	1.0000	1.6207	44	no
2	2	2	4	0	0	600	2	0	0	0	0	1.4551	53	1.0000	1.6286	47	no
2	2	2	17	0	0	600	2	600	17	0	0	1.4569	54	1.0000	1.6671	56	no
2	2	2	17	0	0	0	0	0	0	0	0	1.4601	55	1.0000	1.6131	41	no
2	2	2	7	0	0	600	2	0	0	0	0	1.4604	56	1.0000	1.6387	50	no
2	2	2	17	0	0	600	2	0	0	0	0	1.4763	57	1.0000	1.6675	57	no
2	2	0	0	0	0	0	0	0	0	0	0	1.5440	58	1.0000	1.6978	58	no
2	2	0	0	0	0	600	2	600	32	600	92	1.5464	59	1.0000	1.7411	59	no
2	2	0	0	0	0	600	2	600	32	0	0	1.5464	60	1.0000	1.7411	59	no

15-minute lethal exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	2	0	0	0	0	600	2	0	0	0	0	1.5586	61	1.0000	1.7426	61	no
0	0	0	0	0	0	600	2	600	17	600	32	1.7464	62	1.0000	2.0650	62	yes
0	0	0	0	0	0	600	2	600	17	0	0	1.7613	63	1.0000	2.0888	63	yes
0	0	0	0	0	0	0	0	0	0	0	0	1.7751	64	1.0000	2.2115	65	yes
0	0	0	0	0	0	600	2	0	0	0	0	1.7870	65	1.0000	2.1458	64	yes

Table 17 – Results from 30-minute lethal exposure with IM treatment

30-minute lethal exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	6	4	6	6	1800	2	1800	32	1800	92	1.2048	1	0.7504	1.5509	9	no
6	2	6	4	6	6	1800	2	1800	32	0	0	1.2052	2	0.7559	1.5509	9	no
6	2	6	4	6	6	1800	2	0	0	0	0	1.2262	3	0.8318	1.5509	9	no
6	2	2	4	0	0	1800	2	1800	32	1800	92	1.2753	4	0.9190	1.5701	19	no
6	2	6	4	6	6	0	0	0	0	0	0	1.2753	5	1.0000	1.5402	2	no
6	2	2	4	0	0	1800	2	1800	32	0	0	1.2758	6	0.9255	1.5701	19	no
6	2	2	7	2	12	1800	2	0	0	0	0	1.2810	7	0.9579	1.5729	22	no
6	2	2	4	0	0	1800	2	0	0	0	0	1.2991	8	1.0000	1.5701	19	no
6	2	2	7	0	0	1800	2	0	0	0	0	1.3012	9	1.0000	1.5746	23	no
6	2	0	0	0	0	1800	2	1800	32	1800	92	1.3077	10	0.9945	1.5839	24	no
6	2	0	0	0	0	1800	2	1800	32	0	0	1.3082	11	1.0000	1.5839	24	no
6	2	6	7	0	0	0	0	0	0	0	0	1.3145	12	1.0000	1.5487	4	no
4	2	4	4	4	6	600	2	600	32	600	92	1.3167	13	1.0000	1.5620	15	no
4	2	4	4	4	6	600	2	600	32	0	0	1.3168	14	1.0000	1.5620	15	no
6	2	5	7	0	0	0	0	0	0	0	0	1.3229	15	1.0000	1.5492	5	no
4	2	4	4	4	6	600	2	0	0	0	0	1.3233	16	1.0000	1.5620	15	no
6	2	4	7	0	0	0	0	0	0	0	0	1.3324	17	1.0000	1.5499	7	no
6	2	0	0	0	0	1800	2	0	0	0	0	1.3325	18	1.0000	1.5839	24	no
9	2	0	0	0	0	0	0	0	0	0	0	1.3371	19	1.0000	1.5398	1	no

30-minute lethal exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	3	7	0	0	0	0	0	0	0	0	1.3435	20	1.0000	1.5508	8	no
8	2	0	0	0	0	0	0	0	0	0	0	1.3519	21	1.0000	1.5438	3	no
6	2	2	7	0	0	0	0	0	0	0	0	1.3565	22	1.0000	1.5520	12	no
7	2	0	0	0	0	0	0	0	0	0	0	1.3694	23	1.0000	1.5492	6	no
6	2	1	7	0	0	0	0	0	0	0	0	1.3719	24	1.0000	1.5539	13	no
4	2	2	7	2	12	600	2	0	0	0	0	1.3739	25	1.0000	1.5939	28	no
6	2	0	0	0	0	0	0	0	0	0	0	1.3905	26	1.0000	1.5571	14	no
4	2	2	4	0	0	600	2	600	32	600	92	1.3939	27	1.0000	1.5975	29	no
4	2	2	4	0	0	600	2	600	32	0	0	1.3939	28	1.0000	1.5975	29	no
2	2	2	12	2	22	600	2	600	12	600	22	1.3942	29	1.0000	1.6609	47	no
2	2	2	4	2	6	600	2	600	32	600	92	1.4001	30	1.0000	1.6096	33	no
2	2	2	4	2	6	600	2	600	32	0	0	1.4002	31	1.0000	1.6096	33	no
4	2	2	4	0	0	600	2	0	0	0	0	1.4012	32	1.0000	1.5975	29	no
4	2	2	7	0	0	600	2	0	0	0	0	1.4045	33	1.0000	1.6042	32	no
2	2	2	4	2	6	600	2	0	0	0	0	1.4075	34	1.0000	1.6096	33	no
5	2	0	0	0	0	0	0	0	0	0	0	1.4166	35	1.0000	1.5696	18	no
2	2	2	7	2	12	600	2	0	0	0	0	1.4181	36	1.0000	1.6313	36	no
2	2	2	17	2	32	600	2	600	17	600	32	1.4190	37	1.0000	1.6855	49	no
2	2	2	17	2	32	600	2	600	17	0	0	1.4291	38	1.0000	1.6855	50	no
2	2	2	17	2	32	0	0	0	0	0	0	1.4397	39	1.0000	1.6389	37	no
2	2	2	17	2	32	600	2	0	0	0	0	1.4474	40	1.0000	1.6858	51	no

30-minute lethal exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
4	2	0	0	0	0	600	2	600	32	600	92	1.4483	41	1.0000	1.6418	41	no
4	2	0	0	0	0	600	2	600	32	0	0	1.4484	42	1.0000	1.6418	41	no
2	2	2	12	0	0	600	2	600	12	0	0	1.4487	43	1.0000	1.6703	48	no
4	2	0	0	0	0	0	0	0	0	0	0	1.4495	44	1.0000	1.5922	27	no
2	2	2	4	0	0	600	2	600	32	600	92	1.4526	45	1.0000	1.6496	44	no
2	2	2	4	0	0	600	2	600	32	0	0	1.4526	46	1.0000	1.6496	44	no
4	2	0	0	0	0	600	2	0	0	0	0	1.4562	47	1.0000	1.6416	40	no
2	2	2	4	0	0	600	2	0	0	0	0	1.4605	48	1.0000	1.6494	43	no
2	2	2	17	0	0	600	2	600	17	0	0	1.4626	49	1.0000	1.6869	52	no
2	2	2	7	0	0	600	2	0	0	0	0	1.4656	50	1.0000	1.6594	46	no
2	2	2	17	0	0	0	0	0	0	0	0	1.4749	51	1.0000	1.6390	38	no
2	2	2	17	0	0	600	2	0	0	0	0	1.4816	52	1.0000	1.6883	53	no
3	2	0	0	0	0	0	0	0	0	0	0	1.4926	53	1.0000	1.6407	39	no
2	2	0	0	0	0	600	2	600	32	600	92	1.5476	54	1.0000	1.7656	55	no
2	2	0	0	0	0	600	2	600	32	0	0	1.5476	55	1.0000	1.7656	55	no
2	2	0	0	0	0	0	0	0	0	0	0	1.5545	56	1.0000	1.7498	54	no
2	2	0	0	0	0	600	2	0	0	0	0	1.5594	57	1.0000	1.7677	57	no
1	2	0	0	0	0	0	0	0	0	0	0	1.6367	58	1.0000	1.9520	58	yes
0	0	0	0	0	0	600	2	600	17	600	32	1.7391	59	1.0000	2.0908	59	yes
0	0	0	0	0	0	600	2	600	17	0	0	1.7531	60	1.0000	2.1156	60	yes

30-minute lethal exposure - IM treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
0	0	0	0	0	0	0	0	0	0	0	0	1.7768	61	1.0000	2.2724	62	yes
0	0	0	0	0	0	600	2	0	0	0	0	1.7780	62	1.0000	2.1764	61	yes

Table 18 – Results from 5-minute mild exposure with IV treatment

5-minute mild exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	0	0	1.2403	1	0.8773	1.5297	1	no
6	15-17	6	17-19	6	19-21	3500	15-45	0	0	0	0	1.2404	2	0.8791	1.5297	1	no
6	15-17	2	17-19	0	0	3500	15-45	3500	75-105	0	0	1.2500	3	0.9340	1.5297	1	no
6	15-17	2	17-19	0	0	3500	15-45	0	0	0	0	1.2500	4	0.9360	1.5297	1	no
9	15-25	0	0	0	0	0	0	0	0	0	0	1.2509	5	1.0000	1.5305	19	no
2	15-25	2	30-40	2	45-55	0	0	0	0	0	0	1.2543	6	1.0000	1.5313	32	no
8	15-25	0	0	0	0	0	0	0	0	0	0	1.2543	7	1.0000	1.5306	20	no
7	15-25	0	0	0	0	0	0	0	0	0	0	1.2585	8	1.0000	1.5307	21	no
6	15-25	0	0	0	0	0	0	0	0	0	0	1.2635	9	1.0000	1.5308	22	no
4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	0	0	1.2656	10	1.0000	1.5298	7	no
4	15-17	4	17-19	4	19-21	1750	15-45	0	0	0	0	1.2656	11	1.0000	1.5298	7	no
5	15-25	0	0	0	0	0	0	0	0	0	0	1.2698	12	1.0000	1.5309	23	no
2	15-25	2	30-40	0	0	0	0	0	0	0	0	1.2703	13	1.0000	1.5313	32	no
6	15-17	0	0	0	0	3500	15-45	3500	75-105	0	0	1.2716	14	1.0000	1.5297	1	no
6	15-17	0	0	0	0	3500	15-45	0	0	0	0	1.2716	15	1.0000	1.5297	1	no
4.67	15-25	0	0	0	0	0	0	0	0	0	0	1.2723	16	1.0000	1.5310	24	no
4.33	15-25	0	0	0	0	0	0	0	0	0	0	1.2750	17	1.0000	1.5310	25	no
4	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.2780	18	1.0000	1.5298	7	no
4	15-25	0	0	0	0	0	0	0	0	0	0	1.2780	19	1.0000	1.5310	26	no

5-minute mild exposure - IV treatment																	
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
4	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.2780	20	1.0000	1.5298	7	no
3.67	15-25	0	0	0	0	0	0	0	0	0	0	1.2813	21	1.0000	1.5311	27	no
2	15-25	2	30-40	2	45-55	600	15-45	600	45-75	0	0	1.2824	22	1.0000	1.5313	32	no
2	15-25	2	30-40	2	45-55	600	15-45	0	0	0	0	1.2827	23	1.0000	1.5313	32	no
6	2	2	7-10	0	0	1800	2	1000	62-82	0	0	1.2827	23	1.0000	1.5313	32	no
3.33	15-25	0	0	0	0	0	0	0	0	0	0	1.2850	25	1.0000	1.5311	28	no
2	15-17	2	17-19	2	19-21	1750	15-45	1750	75-105	0	0	1.2867	26	1.0000	1.5304	13	no
2	15-17	2	17-19	2	19-21	1750	15-45	0	0	0	0	1.2868	27	1.0000	1.5304	13	no
3	15-25	0	0	0	0	0	0	0	0	0	0	1.2891	28	1.0000	1.5311	29	no
2.67	15-25	0	0	0	0	0	0	0	0	0	0	1.2938	29	1.0000	1.5312	30	no
2	15-25	2	30-40	0	0	600	15-45	600	45-75	0	0	1.2986	30	1.0000	1.5313	32	no
6	2	2	7-10	2	12-15	1800	2	1000	62-82	0	0	1.2986	30	1.0000	1.5313	32	no
2	15-25	2	30-40	0	0	600	15-45	0	0	0	0	1.2989	32	1.0000	1.5313	32	no
6	2	2	7-10	2	12-15	1800	2	0	0	0	0	1.2989	32	1.0000	1.5313	32	no
2.33	15-25	0	0	0	0	0	0	0	0	0	0	1.2992	34	1.0000	1.5312	31	no
6	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3025	35	1.0000	1.5324	45	no
2	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.3026	36	1.0000	1.5304	13	no
2	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.3027	37	1.0000	1.5304	13	no
4	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.3037	38	1.0000	1.5298	7	no
4	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.3037	39	1.0000	1.5298	7	no
2	15-25	0	0	0	0	0	0	0	0	0	0	1.3054	40	1.0000	1.5313	32	no

5-minute mild exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3086	41	1.0000	1.5324	45	no
4	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3140	42	1.0000	1.5332	48	no
6	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3189	43	1.0000	1.5324	45	no
4	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3228	44	1.0000	1.5332	48	no
2	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3309	45	1.0000	1.5379	51	no
2	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.3317	46	1.0000	1.5304	13	no
2	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.3317	47	1.0000	1.5304	13	no
1	15-25	0	0	0	0	0	0	0	0	0	0	1.3336	48	1.0000	1.5318	44	no
2	15-25	0	0	0	0	600	15-45	0	0	0	0	1.3350	49	1.0000	1.5313	32	no
6	2	2	7-10	0	0	1800	2	0	0	0	0	1.3350	49	1.0000	1.5313	32	no
4	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3389	51	1.0000	1.5332	48	no
2	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3446	52	1.0000	1.5379	51	no
2	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3735	53	1.0000	1.5442	53	no
0	0	0	0	0	0	0	0	0	0	0	0	1.4198	54	1.0000	1.6602	54	no
0	0	0	0	0	0	600	15-45	600	45-75	600	75-105	1.4530	55	1.0000	1.7618	55	no
0	0	0	0	0	0	600	15-45	600	45-75	0	0	1.4532	56	1.0000	1.7630	56	no
0	0	0	0	0	0	600	15-45	0	0	0	0	1.4546	57	1.0000	1.7761	57	no

Table 19 – Results from 15-minute mild exposure with IV treatment

15-minute mild exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	0	0	1.2319	1	0.8711	1.5402	2	no
6	15-17	6	17-19	6	19-21	3500	15-45	0	0	0	0	1.2320	2	0.8743	1.5402	2	no
6	15-17	2	17-19	0	0	3500	15-45	3500	75-105	0	0	1.2427	3	0.9305	1.5402	2	no
6	15-17	2	17-19	0	0	3500	15-45	0	0	0	0	1.2428	4	0.9340	1.5402	2	no
2	15-25	2	30-40	2	45-55	0	0	0	0	0	0	1.2511	5	1.0000	1.5417	20	no
4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	0	0	1.2617	6	1.0000	1.5406	8	no
4	15-17	4	17-19	4	19-21	1750	15-45	0	0	0	0	1.2618	7	1.0000	1.5406	8	no
6	15-17	0	0	0	0	3500	15-45	3500	75-105	0	0	1.2667	8	1.0000	1.5402	2	no
6	15-17	0	0	0	0	3500	15-45	0	0	0	0	1.2668	9	1.0000	1.5402	2	no
2	15-25	2	30-40	0	0	0	0	0	0	0	0	1.2695	10	1.0000	1.5417	20	no
4	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.2756	11	1.0000	1.5406	8	no
4	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.2756	12	1.0000	1.5406	8	no
2	15-25	2	30-40	2	45-55	600	15-45	600	45-75	0	0	1.2820	13	1.0000	1.5417	23	no
6	2	2	7-10	0	0	1800	2	0	0	0	0	1.2824	14	1.0000	1.5313	1	no
2	15-25	2	30-40	2	45-55	600	15-45	0	0	0	0	1.2825	15	1.0000	1.5417	23	no
6	2	2	7-10	2	12-15	1800	2	1000	62-82	0	0	1.2825	15	1.0000	1.5417	23	no
2	15-17	2	17-19	2	19-21	1750	15-45	1750	75-105	0	0	1.2853	17	1.0000	1.5411	14	no
2	15-17	2	17-19	2	19-21	1750	15-45	0	0	0	0	1.2854	18	1.0000	1.5411	14	no
2	15-25	2	30-40	0	0	600	15-45	600	45-75	0	0	1.3006	19	1.0000	1.5417	23	no

15-minute mild exposure - IV treatment																	
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	15-25	2	30-40	0	0	600	15-45	0	0	0	0	1.3011	20	1.0000	1.5417	23	no
6	2	2	7-10	0	0	1800	2	1000	62-82	0	0	1.3011	20	1.0000	1.5417	23	no
6	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3014	22	1.0000	1.5436	31	no
2	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.3029	23	1.0000	1.5411	14	no
2	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.3030	24	1.0000	1.5411	14	no
4	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.3040	25	1.0000	1.5406	8	no
4	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.3041	26	1.0000	1.5406	8	no
6	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3082	27	1.0000	1.5436	31	no
2	15-25	0	0	0	0	0	0	0	0	0	0	1.3084	28	1.0000	1.5417	20	no
4	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3139	29	1.0000	1.5447	34	no
6	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3196	30	1.0000	1.5436	31	no
4	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3237	31	1.0000	1.5447	34	no
2	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3322	32	1.0000	1.5531	37	no
2	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.3347	33	1.0000	1.5411	14	no
2	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.3347	34	1.0000	1.5411	14	no
2	15-25	0	0	0	0	600	15-45	0	0	0	0	1.3410	35	1.0000	1.5417	23	no
6	2	2	7-10	2	12-15	1800	2	0	0	0	0	1.3410	35	1.0000	1.5417	23	no
4	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3415	37	1.0000	1.5447	34	no
2	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3475	38	1.0000	1.5531	37	no
2	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3794	39	1.0000	1.5680	39	no
0	0	0	0	0	0	0	0	0	0	0	0	1.4308	40	1.0000	1.7045	40	no

15-minute mild exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
0	0	0	0	0	0	600	15-45	600	45-75	600	75-105	1.4666	41	1.0000	1.7991	41	no
0	0	0	0	0	0	600	15-45	600	45-75	0	0	1.4669	42	1.0000	1.8007	42	no
0	0	0	0	0	0	600	15-45	0	0	0	0	1.4689	43	1.0000	1.8162	43	no

Table 20 – Results from 30-minute mild exposure with IV treatment

30-minute mild exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	0	0	1.2335	1	0.9063	1.5469	3	no
6	15-17	6	17-19	6	19-21	3500	15-45	0	0	0	0	1.2336	2	0.9084	1.5469	3	no
6	15-17	2	17-19	0	0	3500	15-45	3500	75-105	0	0	1.2432	3	0.9631	1.5469	3	no
6	15-17	2	17-19	0	0	3500	15-45	0	0	0	0	1.2432	4	0.9653	1.5469	3	no
2	15-25	2	30-40	2	45-55	0	0	0	0	0	0	1.2510	5	1.0000	1.5485	21	no
4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	0	0	1.2612	6	1.0000	1.5472	9	no
4	15-17	4	17-19	4	19-21	1750	15-45	0	0	0	0	1.2612	7	1.0000	1.5472	9	no
6	15-17	0	0	0	0	3500	15-45	3500	75-105	0	0	1.2648	8	1.0000	1.5469	3	no
6	15-17	0	0	0	0	3500	15-45	0	0	0	0	1.2648	9	1.0000	1.5469	3	no
2	15-25	2	30-40	0	0	0	0	0	0	0	0	1.2670	10	1.0000	1.5485	21	no
4	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.2736	11	1.0000	1.5472	9	no
4	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.2737	12	1.0000	1.5472	9	no
2	15-25	2	30-40	2	45-55	600	15-45	600	45-75	0	0	1.2805	13	1.0000	1.5485	24	no
2	15-25	2	30-40	2	45-55	600	15-45	0	0	0	0	1.2809	14	1.0000	1.5485	24	no
6	2	2	7-10	2	12-15	1800	2	0	0	0	0	1.2820	15	1.0000	1.5417	1	no
2	15-17	2	17-19	2	19-21	1750	15-45	1750	75-105	0	0	1.2824	16	1.0000	1.5476	15	no
2	15-17	2	17-19	2	19-21	1750	15-45	0	0	0	0	1.2825	17	1.0000	1.5476	15	no
2	15-25	2	30-40	0	0	600	15-45	600	45-75	0	0	1.2967	18	1.0000	1.5485	24	no
2	15-25	2	30-40	0	0	600	15-45	0	0	0	0	1.2972	19	1.0000	1.5485	24	no
6	2	2	7-10	2	12-15	1800	2	1000	62-82	0	0	1.2972	19	1.0000	1.5485	24	no

30-minute mild exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.2984	21	1.0000	1.5476	15	no
2	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.2984	22	1.0000	1.5476	15	no
4	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.2994	23	1.0000	1.5472	9	no
4	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.2994	24	1.0000	1.5472	9	no
6	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3002	25	1.0000	1.5506	31	no
6	2	2	7-10	0	0	1800	2	0	0	0	0	1.3006	26	1.0000	1.5417	1	no
2	15-25	0	0	0	0	0	0	0	0	0	0	1.3025	27	1.0000	1.5485	21	no
6	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3063	28	1.0000	1.5506	31	no
4	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3119	29	1.0000	1.5522	34	no
6	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3167	30	1.0000	1.5506	31	no
4	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3206	31	1.0000	1.5522	34	no
2	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.3275	32	1.0000	1.5476	15	no
2	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.3276	33	1.0000	1.5476	15	no
2	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3289	34	1.0000	1.5635	37	no
2	15-25	0	0	0	0	600	15-45	0	0	0	0	1.3335	35	1.0000	1.5485	24	no
6	2	2	7-10	0	0	1800	2	1000	62-82	0	0	1.3335	35	1.0000	1.5485	24	no
4	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3369	37	1.0000	1.5522	34	no
2	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3427	38	1.0000	1.5635	37	no
2	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3718	39	1.0000	1.5838	39	no
0	0	0	0	0	0	0	0	0	0	0	0	1.4187	40	1.0000	1.7274	40	no

30-minute mild exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
0	0	0	0	0	0	600	15-45	600	45-75	600	75-105	1.4524	41	1.0000	1.8224	41	no
0	0	0	0	0	0	600	15-45	600	45-75	0	0	1.4526	42	1.0000	1.8241	42	no
0	0	0	0	0	0	600	15-45	0	0	0	0	1.4543	43	1.0000	1.8412	43	no

Table 21 – Results from 5-minute severe exposure with IV treatment

5-minute severe exposure - IV treatment																	
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	0	0	1.2017	1	0.7566	1.5823	4	no
6	15-17	6	17-19	6	19-21	3500	15-45	0	0	0	0	1.2036	2	0.7750	1.5823	4	no
6	15-17	2	17-19	0	0	3500	15-45	3500	75-105	0	0	1.2234	3	0.8339	1.5823	4	no
6	15-17	2	17-19	0	0	3500	15-45	0	0	0	0	1.2254	4	0.8537	1.5823	4	no
4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	0	0	1.2679	5	0.9636	1.5826	10	no
6	15-17	0	0	0	0	3500	15-45	3500	75-105	0	0	1.2694	6	0.9867	1.5823	4	no
4	15-17	4	17-19	4	19-21	1750	15-45	0	0	0	0	1.2695	7	0.9818	1.5826	10	no
6	15-17	0	0	0	0	3500	15-45	0	0	0	0	1.2717	8	1.0000	1.5823	4	no
9	15-25	0	0	0	0	0	0	0	0	0	0	1.2794	9	1.0000	1.5830	22	no
6	2	2	7-10	0	0	1800	2	1000	62-82	0	0	1.2805	10	1.0000	1.5485	1	no
6	2	2	7-10	0	0	1800	2	0	0	0	0	1.2809	11	1.0000	1.5485	1	no
2	15-25	2	30-40	2	45-55	0	0	0	0	0	0	1.2843	12	1.0000	1.5851	29	no
8	15-25	0	0	0	0	0	0	0	0	0	0	1.2875	13	1.0000	1.5831	23	no
4	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.2953	14	1.0000	1.5826	10	no
6	2	2	7-10	2	12-15	1800	2	0	0	0	0	1.2967	15	1.0000	1.5485	1	no
7	15-25	0	0	0	0	0	0	0	0	0	0	1.2970	16	1.0000	1.5831	24	no
4	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.2970	17	1.0000	1.5826	10	no
6	15-25	0	0	0	0	0	0	0	0	0	0	1.3083	18	1.0000	1.5832	25	no
2	15-17	2	17-19	2	19-21	1750	15-45	1750	75-105	0	0	1.3144	19	1.0000	1.5830	16	no

5-minute severe exposure - IV treatment																	
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	15-17	2	17-19	2	19-21	1750	15-45	0	0	0	0	1.3162	20	1.0000	1.5830	16	no
2	15-25	2	30-40	2	45-55	600	15-45	600	45-75	0	0	1.3212	21	1.0000	1.5851	32	no
5	15-25	0	0	0	0	0	0	0	0	0	0	1.3223	22	1.0000	1.5833	26	no
2	15-25	2	30-40	0	0	0	0	0	0	0	0	1.3241	23	1.0000	1.5851	29	no
6	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3249	24	1.0000	1.5907	38	no
6	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3384	25	1.0000	1.5907	38	no
4	15-25	0	0	0	0	0	0	0	0	0	0	1.3398	26	1.0000	1.5838	27	no
4	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3457	27	1.0000	1.5997	41	no
2	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.3469	28	1.0000	1.5830	16	no
4	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.3488	29	1.0000	1.5826	10	no
2	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.3488	30	1.0000	1.5830	16	no
4	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.3507	31	1.0000	1.5826	10	no
6	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3599	32	1.0000	1.5907	38	no
2	15-25	2	30-40	2	45-55	600	15-45	0	0	0	0	1.3607	33	1.0000	1.5851	32	no
2	15-25	2	30-40	0	0	600	15-45	600	45-75	0	0	1.3607	33	1.0000	1.5851	32	no
3	15-25	0	0	0	0	0	0	0	0	0	0	1.3628	35	1.0000	1.5844	28	no
2	15-25	2	30-40	0	0	600	15-45	0	0	0	0	1.3645	36	1.0000	1.5851	32	no
4	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3650	37	1.0000	1.5997	41	no
2	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3759	38	1.0000	1.6215	44	no
2	15-25	0	0	0	0	0	0	0	0	0	0	1.3951	39	1.0000	1.5851	29	no
4	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3985	40	1.0000	1.6062	43	no

5-minute severe exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.4024	41	1.0000	1.5830	16	no
2	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.4045	42	1.0000	1.5830	16	no
2	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4061	43	1.0000	1.6242	45	no
2	15-25	0	0	0	0	600	15-45	0	0	0	0	1.4364	44	1.0000	1.5851	32	no
6	2	2	7-10	2	12-15	1800	2	1000	62-82	0	0	1.4364	44	1.0000	1.5851	32	no
1	15-25	0	0	0	0	0	0	0	0	0	0	1.4469	46	1.0000	1.6396	46	no
2	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.4653	47	1.0000	1.6618	47	no
0	0	0	0	0	0	0	0	0	0	0	0	1.5841	48	1.0000	1.9020	48	yes
0	0	0	0	0	0	600	15-45	600	45-75	600	75-105	1.6150	49	1.0000	1.9244	49	yes
0	0	0	0	0	0	600	15-45	600	45-75	0	0	1.6178	50	1.0000	1.9267	50	yes
0	0	0	0	0	0	600	15-45	0	0	0	0	1.6270	51	1.0000	1.9505	51	yes

Table 22 – Results from 15-minute severe exposure with IV treatment

15-minute severe exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	0	0	1.2088	1	0.7827	1.5838	1	no
6	15-17	6	17-19	6	19-21	3500	15-45	0	0	0	0	1.2102	2	0.7993	1.5838	1	no
6	15-17	2	17-19	0	0	3500	15-45	3500	75-105	0	0	1.2286	3	0.8576	1.5838	1	no
6	15-17	2	17-19	0	0	3500	15-45	0	0	0	0	1.2302	4	0.8755	1.5838	1	no
4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	0	0	1.2704	5	0.9893	1.5838	7	no
6	15-17	0	0	0	0	3500	15-45	3500	75-105	0	0	1.2707	6	1.0000	1.5838	1	no
4	15-17	4	17-19	4	19-21	1750	15-45	0	0	0	0	1.2716	7	1.0000	1.5838	7	no
6	15-17	0	0	0	0	3500	15-45	0	0	0	0	1.2725	8	1.0000	1.5838	1	no
2	15-25	2	30-40	2	45-55	0	0	0	0	0	0	1.2833	9	1.0000	1.5872	23	no
4	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.2955	10	1.0000	1.5838	7	no
4	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.2967	11	1.0000	1.5838	7	no
2	15-17	2	17-19	2	19-21	1750	15-45	1750	75-105	0	0	1.3130	12	1.0000	1.5849	13	no
2	15-17	2	17-19	2	19-21	1750	15-45	0	0	0	0	1.3143	13	1.0000	1.5849	13	no
2	15-25	2	30-40	2	45-55	600	15-45	600	45-75	0	0	1.3194	14	1.0000	1.5872	26	no
2	15-25	2	30-40	0	0	0	0	0	0	0	0	1.3196	15	1.0000	1.5872	23	no
6	2	2	7-10	2	12-15	1800	2	1000	62-82	0	0	1.3212	16	1.0000	1.5851	19	no
2	15-25	2	30-40	2	45-55	600	15-45	0	0	0	0	1.3223	17	1.0000	1.5872	26	no
6	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3262	18	1.0000	1.5935	31	no
6	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3386	19	1.0000	1.5935	31	no

15-minute severe exposure - IV treatment																	
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)						Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.3430	20	1.0000	1.5849	13	no
2	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.3444	21	1.0000	1.5849	13	no
4	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.3447	22	1.0000	1.5838	7	no
4	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3457	23	1.0000	1.6033	34	no
4	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.3461	24	1.0000	1.5838	7	no
2	15-25	2	30-40	0	0	600	15-45	600	45-75	0	0	1.3554	25	1.0000	1.5872	26	no
6	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3584	26	1.0000	1.5935	33	no
2	15-25	2	30-40	0	0	600	15-45	0	0	0	0	1.3587	27	1.0000	1.5872	26	no
6	2	2	7-10	2	12-15	1800	2	0	0	0	0	1.3607	28	1.0000	1.5851	19	no
6	2	2	7-10	0	0	1800	2	1000	62-82	0	0	1.3607	28	1.0000	1.5851	19	no
4	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3634	30	1.0000	1.6033	35	no
6	2	2	7-10	0	0	1800	2	0	0	0	0	1.3645	31	1.0000	1.5851	19	no
2	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3740	32	1.0000	1.6256	37	no
2	15-25	0	0	0	0	0	0	0	0	0	0	1.3856	33	1.0000	1.5872	23	no
4	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3943	34	1.0000	1.6106	36	no
2	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.3946	35	1.0000	1.5849	13	no
2	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.3962	36	1.0000	1.5849	13	no
2	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4017	37	1.0000	1.6287	38	no
2	15-25	0	0	0	0	600	15-45	0	0	0	0	1.4255	38	1.0000	1.5872	26	no
2	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.4564	39	1.0000	1.6674	39	no
0	0	0	0	0	0	0	0	0	0	0	0	1.5653	40	1.0000	1.9094	40	yes

15-minute severe exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
0	0	0	0	0	0	600	15-45	600	45-75	600	75-105	1.5966	41	1.0000	1.9318	41	yes
0	0	0	0	0	0	600	15-45	600	45-75	0	0	1.5988	42	1.0000	1.9342	42	yes
0	0	0	0	0	0	600	15-45	0	0	0	0	1.6069	43	1.0000	1.9585	43	yes

Table 23 – Results from 30-minute severe exposure with IV treatment

30-minute severe exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	0	0	1.2201	1	0.8319	1.5838	1	no
6	15-17	6	17-19	6	19-21	3500	15-45	0	0	0	0	1.2209	2	0.8443	1.5838	1	no
6	15-17	2	17-19	0	0	3500	15-45	3500	75-105	0	0	1.2366	3	0.9022	1.5838	1	no
6	15-17	2	17-19	0	0	3500	15-45	0	0	0	0	1.2375	4	0.9154	1.5838	1	no
6	15-17	0	0	0	0	3500	15-45	3500	75-105	0	0	1.2721	5	1.0000	1.5838	1	no
4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	0	0	1.2724	6	1.0000	1.5838	7	no
4	15-17	4	17-19	4	19-21	1750	15-45	0	0	0	0	1.2730	7	1.0000	1.5838	7	no
6	15-17	0	0	0	0	3500	15-45	0	0	0	0	1.2731	8	1.0000	1.5838	1	no
2	15-25	2	30-40	2	45-55	0	0	0	0	0	0	1.2778	9	1.0000	1.5869	19	no
4	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.2933	10	1.0000	1.5838	7	no
4	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.2939	11	1.0000	1.5838	7	no
2	15-25	2	30-40	0	0	0	0	0	0	0	0	1.3076	12	1.0000	1.5869	19	no
2	15-17	2	17-19	2	19-21	1750	15-45	1750	75-105	0	0	1.3080	13	1.0000	1.5845	13	no
2	15-17	2	17-19	2	19-21	1750	15-45	0	0	0	0	1.3086	14	1.0000	1.5845	13	no
2	15-25	2	30-40	2	45-55	600	15-45	600	45-75	0	0	1.3126	15	1.0000	1.5869	22	no
2	15-25	2	30-40	2	45-55	600	15-45	0	0	0	0	1.3146	16	1.0000	1.5869	22	no
6	2	2	7-10	0	0	1800	2	1000	62-82	0	0	1.3223	17	1.0000	1.5872	27	no
6	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3247	18	1.0000	1.5933	31	no
2	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.3335	19	1.0000	1.5845	13	no

30-minute severe exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.3342	20	1.0000	1.5845	13	no
6	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3349	21	1.0000	1.5933	31	no
4	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.3351	22	1.0000	1.5838	7	no
4	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.3357	23	1.0000	1.5838	7	no
4	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3417	24	1.0000	1.6033	34	no
2	15-25	2	30-40	0	0	600	15-45	600	45-75	0	0	1.3424	25	1.0000	1.5869	22	no
2	15-25	2	30-40	0	0	600	15-45	0	0	0	0	1.3446	26	1.0000	1.5869	22	no
6	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3517	27	1.0000	1.5933	33	no
6	2	2	7-10	2	12-15	1800	2	1000	62-82	0	0	1.3554	28	1.0000	1.5872	27	no
4	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3564	29	1.0000	1.6033	35	no
6	2	2	7-10	2	12-15	1800	2	0	0	0	0	1.3587	30	1.0000	1.5872	27	no
2	15-25	0	0	0	0	0	0	0	0	0	0	1.3642	31	1.0000	1.5869	19	no
2	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3665	32	1.0000	1.6257	37	no
2	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.3782	33	1.0000	1.5845	13	no
2	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.3789	34	1.0000	1.5845	13	no
4	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.3826	35	1.0000	1.6108	36	no
2	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.3896	36	1.0000	1.6290	38	no
2	15-25	0	0	0	0	600	15-45	0	0	0	0	1.4020	37	1.0000	1.5869	22	no
6	2	2	7-10	0	0	1800	2	0	0	0	0	1.4255	38	1.0000	1.5872	27	no
2	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.4361	39	1.0000	1.6680	39	no
0	0	0	0	0	0	0	0	0	0	0	0	1.5254	40	1.0000	1.9011	40	yes

30-minute severe exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
0	0	0	0	0	0	600	15-45	600	45-75	600	75-105	1.5582	41	1.0000	1.9329	41	yes
0	0	0	0	0	0	600	15-45	600	45-75	0	0	1.5596	42	1.0000	1.9353	42	yes
0	0	0	0	0	0	600	15-45	0	0	0	0	1.5655	43	1.0000	1.9599	43	yes

Table 24 – Results from 5-minute lethal exposure with IV treatment

5-minute lethal exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	0	0	1.2084	1	0.7284	1.6450	5	no
6	15-17	6	17-19	6	19-21	3500	15-45	0	0	0	0	1.2132	2	0.7570	1.6450	5	no
6	15-17	2	17-19	0	0	3500	15-45	3500	75-105	0	0	1.2382	3	0.8146	1.6450	5	no
6	15-17	2	17-19	0	0	3500	15-45	0	0	0	0	1.2434	4	0.8457	1.6450	5	no
6	15-17	0	0	0	0	3500	15-45	3500	75-105	0	0	1.2998	5	0.9808	1.6450	5	no
6	15-17	0	0	0	0	3500	15-45	0	0	0	0	1.3057	6	1.0000	1.6450	5	no
4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	0	0	1.3093	7	0.9688	1.6459	11	no
4	15-17	4	17-19	4	19-21	1750	15-45	0	0	0	0	1.3138	8	1.0000	1.6459	11	no
6	2	2	7-10	2	12-15	1800	2	1000	62-82	0	0	1.3146	9	1.0000	1.5869	1	no
6	2	2	7-10	0	0	1800	2	0	0	0	0	1.3194	10	1.0000	1.5872	4	no
6	2	2	7-10	0	0	1800	2	1000	62-82	0	0	1.3446	11	1.0000	1.5869	1	no
4	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.3467	12	1.0000	1.6459	11	no
4	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.3516	13	1.0000	1.6459	11	no
2	15-17	2	17-19	2	19-21	1750	15-45	1750	75-105	0	0	1.3729	14	1.0000	1.6474	17	no
2	15-17	2	17-19	2	19-21	1750	15-45	0	0	0	0	1.3780	15	1.0000	1.6474	17	no
6	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3858	16	1.0000	1.6828	36	no
9	15-25	0	0	0	0	0	0	0	0	0	0	1.3876	17	1.0000	1.6476	23	no
2	15-25	2	30-40	2	45-55	0	0	0	0	0	0	1.3969	18	1.0000	1.6525	30	no
8	15-25	0	0	0	0	0	0	0	0	0	0	1.3993	19	1.0000	1.6478	24	no

5-minute lethal exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	2	2	7-10	2	12-15	1800	2	0	0	0	0	1.4020	20	1.0000	1.5869	1	no
2	15-25	2	30-40	2	45-55	600	15-45	600	45-75	0	0	1.4034	21	1.0000	1.6527	32	no
6	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4045	22	1.0000	1.6834	37	no
2	15-25	2	30-40	2	45-55	600	15-45	0	0	0	0	1.4118	23	1.0000	1.6527	32	no
4	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.4128	24	1.0000	1.6999	39	no
7	15-25	0	0	0	0	0	0	0	0	0	0	1.4130	25	1.0000	1.6480	25	no
2	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.4161	26	1.0000	1.6474	17	no
4	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.4181	27	1.0000	1.6459	11	no
2	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.4216	28	1.0000	1.6474	17	no
4	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.4236	29	1.0000	1.6459	11	no
6	15-25	0	0	0	0	0	0	0	0	0	0	1.4293	30	1.0000	1.6483	26	no
6	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.4338	31	1.0000	1.6901	38	no
4	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4396	32	1.0000	1.7025	40	no
5	15-25	0	0	0	0	0	0	0	0	0	0	1.4491	33	1.0000	1.6487	27	no
2	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.4520	34	1.0000	1.7286	43	no
2	15-25	2	30-40	0	0	0	0	0	0	0	0	1.4533	35	1.0000	1.6525	30	no
2	15-25	2	30-40	0	0	600	15-45	600	45-75	0	0	1.4576	36	1.0000	1.6527	32	no
2	15-25	2	30-40	0	0	600	15-45	0	0	0	0	1.4667	37	1.0000	1.6527	32	no
4	15-25	0	0	0	0	0	0	0	0	0	0	1.4738	38	1.0000	1.6496	28	no
4	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.4850	39	1.0000	1.7197	42	no
2	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.4879	40	1.0000	1.6474	17	no

5-minute lethal exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4936	41	1.0000	1.7385	44	no
2	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.4940	42	1.0000	1.6474	17	no
3	15-25	0	0	0	0	0	0	0	0	0	0	1.5059	43	1.0000	1.6506	29	no
2	15-25	0	0	0	0	0	0	0	0	0	0	1.5502	44	1.0000	1.7599	45	no
2	15-25	0	0	0	0	600	15-45	0	0	0	0	1.5615	45	1.0000	1.7190	41	no
2	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.5733	46	1.0000	1.7913	46	no
1	15-25	0	0	0	0	0	0	0	0	0	0	1.6195	47	1.0000	1.9132	47	yes
0	0	0	0	0	0	600	15-45	600	45-75	600	75-105	1.7671	48	1.0000	2.0804	48	yes
0	0	0	0	0	0	600	15-45	600	45-75	0	0	1.7737	49	1.0000	2.0835	49	yes
0	0	0	0	0	0	600	15-45	0	0	0	0	1.7932	50	1.0000	2.1168	50	yes
0	0	0	0	0	0	0	0	0	0	0	0	1.7948	51	1.0000	2.2021	51	yes

Table 25 – Results from 15-minute lethal exposure with IV treatment

15-minute lethal exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	0	0	1.2153	1	0.7469	1.6476	2	no
6	15-17	6	17-19	6	19-21	3500	15-45	0	0	0	0	1.2195	2	0.7747	1.6476	2	no
6	15-17	2	17-19	0	0	3500	15-45	3500	75-105	0	0	1.2434	3	0.8315	1.6476	2	no
6	15-17	2	17-19	0	0	3500	15-45	0	0	0	0	1.2479	4	0.8617	1.6476	2	no
6	15-17	0	0	0	0	3500	15-45	3500	75-105	0	0	1.3018	5	0.9961	1.6476	2	no
6	15-17	0	0	0	0	3500	15-45	0	0	0	0	1.3070	6	1.0000	1.6476	2	no
4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	0	0	1.3118	7	0.9888	1.6484	8	no
4	15-17	4	17-19	4	19-21	1750	15-45	0	0	0	0	1.3156	8	1.0000	1.6484	8	no
6	2	2	7-10	0	0	1800	2	0	0	0	0	1.3424	9	1.0000	1.5869	1	no
4	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.3471	10	1.0000	1.6484	8	no
4	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.3513	11	1.0000	1.6484	8	no
2	15-17	2	17-19	2	19-21	1750	15-45	1750	75-105	0	0	1.3718	12	1.0000	1.6496	14	no
2	15-17	2	17-19	2	19-21	1750	15-45	0	0	0	0	1.3762	13	1.0000	1.6496	14	no
6	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.3871	14	1.0000	1.6869	28	no
2	15-25	2	30-40	2	45-55	0	0	0	0	0	0	1.3935	15	1.0000	1.6550	22	no
2	15-25	2	30-40	2	45-55	600	15-45	600	45-75	0	0	1.4010	16	1.0000	1.6551	24	no
6	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4047	17	1.0000	1.6875	29	no
2	15-25	2	30-40	2	45-55	600	15-45	0	0	0	0	1.4086	18	1.0000	1.6551	24	no
6	2	2	7-10	2	12-15	1800	2	1000	62-82	0	0	1.4118	19	1.0000	1.6527	20	no

15-minute lethal exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
2	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.4128	20	1.0000	1.6496	14	no
4	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.4129	21	1.0000	1.7041	31	no
4	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.4150	22	1.0000	1.6484	8	no
2	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.4175	23	1.0000	1.6496	14	no
4	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.4197	24	1.0000	1.6484	8	no
6	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.4324	25	1.0000	1.6945	30	no
4	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4381	26	1.0000	1.7069	32	no
2	15-25	2	30-40	0	0	0	0	0	0	0	0	1.4467	27	1.0000	1.6550	22	no
2	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.4503	28	1.0000	1.7331	36	no
2	15-25	2	30-40	0	0	600	15-45	600	45-75	0	0	1.4522	29	1.0000	1.6551	24	no
2	15-25	2	30-40	0	0	600	15-45	0	0	0	0	1.4605	30	1.0000	1.6551	24	no
6	2	2	7-10	0	0	1800	2	1000	62-82	0	0	1.4667	31	1.0000	1.6527	20	no
4	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.4810	32	1.0000	1.7245	34	no
2	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.4816	33	1.0000	1.6496	14	no
2	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.4868	34	1.0000	1.6496	14	no
2	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4895	35	1.0000	1.7432	37	no
2	15-25	0	0	0	0	0	0	0	0	0	0	1.5389	36	1.0000	1.7673	38	no
2	15-25	0	0	0	0	600	15-45	0	0	0	0	1.5508	37	1.0000	1.7254	35	no
6	2	2	7-10	2	12-15	1800	2	0	0	0	0	1.5615	38	1.0000	1.7190	33	no
2	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.5651	39	1.0000	1.7966	39	no
0	0	0	0	0	0	600	15-45	600	45-75	600	75-105	1.7507	40	1.0000	2.0863	40	yes

15-minute lethal exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
0	0	0	0	0	0	600	15-45	600	45-75	0	0	1.7566	41	1.0000	2.0895	41	yes
0	0	0	0	0	0	600	15-45	0	0	0	0	1.7746	42	1.0000	2.1232	42	yes
0	0	0	0	0	0	0	0	0	0	0	0	1.7751	43	1.0000	2.2115	43	yes

Table 26 – Results from 30-minute lethal exposure with IV treatment

30-minute lethal exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
6	15-17	6	17-19	6	19-21	3500	15-45	3500	75-105	0	0	1.2315	1	0.7780	1.6627	4	no
6	15-17	6	17-19	6	19-21	3500	15-45	0	0	0	0	1.2353	2	0.8055	1.6627	4	no
6	15-17	2	17-19	0	0	3500	15-45	3500	75-105	0	0	1.2577	3	0.8609	1.6627	4	no
6	15-17	2	17-19	0	0	3500	15-45	0	0	0	0	1.2617	4	0.8906	1.6627	4	no
6	15-17	0	0	0	0	3500	15-45	3500	75-105	0	0	1.3124	5	1.0000	1.6627	4	no
6	15-17	0	0	0	0	3500	15-45	0	0	0	0	1.3169	6	1.0000	1.6627	4	no
4	15-17	4	17-19	4	19-21	1750	15-45	1750	75-105	0	0	1.3251	7	1.0000	1.6636	10	no
4	15-17	4	17-19	4	19-21	1750	15-45	0	0	0	0	1.3284	8	1.0000	1.6636	10	no
4	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.3582	9	1.0000	1.6636	10	no
4	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.3618	10	1.0000	1.6636	10	no
2	15-17	2	17-19	2	19-21	1750	15-45	1750	75-105	0	0	1.3814	11	1.0000	1.6652	16	no
2	15-17	2	17-19	2	19-21	1750	15-45	0	0	0	0	1.3851	12	1.0000	1.6652	16	no
6	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.4007	13	1.0000	1.7099	28	no
6	2	2	7-10	2	12-15	1800	2	0	0	0	0	1.4034	14	1.0000	1.6527	1	no
2	15-25	2	30-40	2	45-55	0	0	0	0	0	0	1.4094	15	1.0000	1.6715	22	no
2	15-25	2	30-40	2	45-55	600	15-45	600	45-75	0	0	1.4117	16	1.0000	1.6720	24	no
6	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4172	17	1.0000	1.7109	29	no
2	15-25	2	30-40	2	45-55	600	15-45	0	0	0	0	1.4188	18	1.0000	1.6720	24	no
2	15-17	2	17-19	0	0	1750	15-45	1750	75-105	0	0	1.4201	19	1.0000	1.6652	16	no

30-minute lethal exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
4	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.4219	20	1.0000	1.6636	10	no
2	15-17	2	17-19	0	0	1750	15-45	0	0	0	0	1.4241	21	1.0000	1.6652	16	no
4	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.4253	22	1.0000	1.7279	32	no
4	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.4259	23	1.0000	1.6636	10	no
6	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.4433	24	1.0000	1.7188	30	no
4	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4490	25	1.0000	1.7314	33	no
6	2	2	7-10	0	0	1800	2	0	0	0	0	1.4576	26	1.0000	1.6527	1	no
2	15-25	2	30-40	0	0	0	0	0	0	0	0	1.4595	27	1.0000	1.6715	22	no
2	15-25	2	30-40	0	0	600	15-45	600	45-75	0	0	1.4597	28	1.0000	1.6720	24	no
6	2	2	7-10	2	12-15	1800	2	1000	62-82	0	0	1.4605	29	1.0000	1.6551	3	no
2	15-17	2	20-22	2	25-27	1000	15-45	0	0	0	0	1.4610	30	1.0000	1.7579	36	no
2	15-25	2	30-40	0	0	600	15-45	0	0	0	0	1.4674	31	1.0000	1.6720	24	no
2	15-17	0	0	0	0	1750	15-45	1750	75-105	0	0	1.4852	32	1.0000	1.6652	16	no
4	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.4894	33	1.0000	1.7502	34	no
2	15-17	0	0	0	0	1750	15-45	0	0	0	0	1.4896	34	1.0000	1.6652	16	no
2	15-17	2	20-22	0	0	1000	15-45	0	0	0	0	1.4978	35	1.0000	1.7691	37	no
2	15-25	0	0	0	0	0	0	0	0	0	0	1.5473	36	1.0000	1.8185	38	no
6	2	2	7-10	0	0	1800	2	1000	62-82	0	0	1.5508	37	1.0000	1.7254	31	no
2	15-25	0	0	0	0	600	15-45	0	0	0	0	1.5531	38	1.0000	1.7572	35	no
2	15-17	0	0	0	0	1000	15-45	0	0	0	0	1.5691	39	1.0000	1.8244	39	no
0	0	0	0	0	0	600	15-45	600	45-75	600	75-105	1.7466	40	1.0000	2.1178	40	yes

30-minute lethal exposure - IV treatment												Normalized Area Under the Curve	Area Rank	Symptom Minimum	Symptom Maximum	Symptom Rank	Death Occurs
Atropine - dose amount and timing (mg, min)						Oxime - dose amount and timing (mg, min)											
Dose 1		Dose 2		Dose 3		Dose 1		Dose 2		Dose 3							
0	0	0	0	0	0	600	15-45	600	45-75	0	0	1.7518	41	1.0000	2.1211	41	yes
0	0	0	0	0	0	600	15-45	0	0	0	0	1.7686	42	1.0000	2.1565	42	yes
0	0	0	0	0	0	0	0	0	0	0	0	1.7768	43	1.0000	2.2724	43	yes

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14. ABSTRACT

Organophosphates such as nerve agents have been used on several occasions in the past to inflict harm upon military and civilian populations in various parts of the world. The threat of these chemicals use against the military and civilians continues today, and the suggested treatment guidelines available may be ineffective or possibly cause harm. The guidelines investigated during the research presented here all included the use of two antidotes, atropine and oxime. The efficacy of oximes has been questioned and it has been suggested that they may cause harm to the patient. Both atropine and oxime are issued to military members for self-treatment following nerve agent exposure. Additionally, civilian medical facilities have access to both antidotes to treat patients exposed to nerve agents or organophosphate-based pesticides. The research presented here used a physiologically-based pharmacokinetic model to determine an optimal treatment strategy for exposures to organophosphates. Results from the model suggest that the treatment of organophosphate poisoning according to current guidance has the potential to increase the severity of symptoms that a patient is experiencing. The results presented indicate that oxime use is beneficial when the patient has been exposed to a weak organophosphate such as a pesticide, but not as prescribed in current guidance. Additionally, results indicate that in scenarios involving strong organophosphates such as nerve agents, oxime use is ineffective and has the potential to increase the severity of symptoms. Finally, the model was used to determine an optimal dosing strategy for treatment of organophosphate poisoning that varies significantly from the guidance currently available.

15. SUBJECT TERMS
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